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DIAGNOSTIC APPLICATION OF STUDY OF BONE MARROW IN INFANTS AND IN CHILDREN

HENRY G. PONCHER, M.D.
CHICAGO

DR. ZUELZER'S excellent discussion of the normal and the pathologic physiology of bone marrow provides a rational basis for applying this information to a clinical setting.

Historically, the conception of bone marrow as a functioning tissue is of relatively recent date. It was regarded as performing the purely mechanical function of filling the medullary cavity of the bones until about eighty years ago, when Neumann contended it functioned as a site of blood formation in postnatal life. Postmortem investigation of the effects of various diseases of the bone marrow soon followed. Lack of correlation and apparently conflicting findings in examination of the blood during life and changes in the bone marrow after death led to attempts to study bone marrow in living patients by means of surgical biopsy.

Originally, biopsy of the bone marrow was mainly undertaken as an alternative method of splenic puncture in the diagnosis of malaria and leishmaniasis. Later it was appreciated that sections and smears of the curetted marrow of the tibia and femur yielded important diagnostic information in disease. Seyfarth's description[1] of the method of trephining the more accessible sternum, in 1923, was a definite impetus to the more frequent clinical use of investigation of bone marrow. However, as Dr. Zuelzer has pointed out, the introduction of a simple and harmless technic of sternal puncture by Arinkin[2] in 1927 further extended the clinical employment of study of the bone marrow as a practical diagnostic procedure.

A consideration of the relative merits of sternal puncture and trephine or the evaluation of the numerous modifications of both technics which have been advocated[3] is not within the scope of this presentation. It

From the Department of Pediatrics, University of Illinois College of Medicine.

1. Seyfarth, C.: Diagnostic Trepanation of Sternum, Deutsche med. Wchnschr. **49**:180-181 (Feb. 9) 1923.

2. Arinkin, M. I.: Methodology of Examining Bone Marrow in Live Patients, with Hematopoietic Diseases, Vestnik khir. (no. 30) **10**:57-60, 1927.

3. Dameshek, H.; Henstell, H. H., and Valentine, E.: Comparative Value and Limitations of Trephine and Puncture Methods for Biopsy of Sternal Bone Marrow, Ann. Int. Med. **11**:801-818 (Nov.) 1937.

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may be of interest, however, to consider briefly some of the practical aspects of the technic of studying the bone marrow before discussing the diagnostic application of the procedure in diseases of the blood-forming organs in infants and in children.

METHODS OF STUDYING BONE MARROW

The two methods in general use in the study of bone marrow are trephine, essentially a surgical procedure, and sternal aspiration, a simple bedside or office procedure which is practical and informative from a clinical point of view.

The specimen obtained by trephine may be studied as tissue sections, smears, imprint and serum suspension preparations. The advantage claimed for trephination methods is that bone marrow may be obtained undiluted with blood and with its histologic relations undisturbed. Its routine clinical use is limited by the fact that it is essentially a surgical procedure, repeated observations on the same person are limited, and scars resulting from the procedure are of esthetic importance in female patients.

The ease and simplicity of sternal puncture make this procedure most acceptable for routine clinical study. The material obtained by sternal aspiration may be used in making counts, smears on slides or cover slips, supravital study and marrow culture. The last two methods of study are not practical for routine work.

Study of the concentration of marrow cells is the method that my colleagues and I have used in our routine work and has been described in detail previously.[4] This procedure has proved most satisfactory for routine study. When only small amounts of marrow are available, as in young infants, the use of direct smears of the marrow may be more feasible.

SITE FOR DIAGNOSTIC PUNCTURE

The accessibility of the sternum because of its superficial location and the fact that it remains actively hematopoietic throughout life make this area an ideal site for diagnostic puncture. The observation that the sternal marrow functions as a lifelong site of hematopoiesis is of greater importance in older children and adults than it is in infants and young children whose tibial marrow is satisfactory for biopsy at least until 7 or 8 years of age (the time when fatty metamorphosis begins at this site). Furthermore, with more frequent use of the tibial or femoral site for infusions and transfusions it may be practical to employ diagnostic aspirations of tibial or femoral marrow where the marrow cavity has been penetrated for some other purposes. Tibial or femoral puncture can be advocated with more safety for the novice than sternal aspiration, espe-

4. Limarzi, L. R.: Diagnostic Value of Sternal Marrow Aspirations, Illinois M. J. 75:38-46 (Jan.) 1939.

cially in young infants, because of the thinness of the sternal plate and the sparse distribution of the sternal marrow. In general, however, the sternum is an ideal site for diagnostic puncture at most age periods.

In the performance of sternal puncture in infants and young children knowledge of a few practical facts concerning the development of the human sternum are important.

The mature sternum consists of (1) the manubrium, (2) the gladiolus or body consisting of sternebrae which have fused and (3) the xiphisternum. Segments bearing the ossification centers are known as sternebrae. In fetal life the sternum develops as paired longitudinal cartilaginous bars that unite from above downward. Accordingly, in performing sternal aspiration one should avoid the midline as it is in this area that fusion may be incomplete in about 20 per cent of the cases. The incidence of incomplete fusion is also higher in the distal portion of the sternum, and this area is also thinner. One should therefore avoid puncturing the sternum in its lower half. At birth the ossification centers of the manubrium are fused into one large center, and this may be the first sternal area where sufficient marrow is available for aspiration in the neonatal period. One may elect to aspirate at this site in very young infants instead of the conventional place between the second and third ribs in the body of the sternum. Great care must, however, be exercised in electing this site as the spongiosa is thin in the center and therefore easily perforated. Occasionally, episternal centers are found in the manubrium on either side of the jugular notch which are vestigeal. The manubrium may occasionally have two to three or even five centers. When two are present they are situated one above the other, the upper one being the larger.

The second sternebra in the body of the sternum seldom has more than one center. From this point on the ossification progresses in a distal manner with paired centers, placed laterally, uniting to form a larger center in each segment of the sternum until the age of about 10 years, when the marrow cavity of the sternum is filled completely.

It is preferable, therefore, to insert the sternal needle slightly lateral to the midline before the age of 10 to 12 years, as one is more apt to hit the ossification center containing marrow while avoiding the thinner portion of the midline region. Variations in the number and location of ossification centers containing marrow are not uncommon, and this should be cosidered when aspiration is unsuccessful.

The most accessible site for aspiration of sternal marrow, excepting the neonatal period, is just below the sternomanubrial ridge in the second interspace between the second and third ribs, slightly lateral to the midline. It is important to remember that the area between the sternebrae is cartilaginous, and it is for this reason that the needle should be inserted opposite an interspace instead of a rib in children. While perforation of the posterior lamina of the sternum is not as serious

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in infants with their cylindric chests as it is in older children and adults in whom the anterior posterior diameter of the chest is relatively decreased, it is always a potential source of complications.

Knowledge of the thickness of the sternum at various ages is essential as a guide for the insertion of the sternal needle to the correct depth. A large number of specimens have not been studied,[5] but from the material available it may be stated that the entire thickness of the sternum varies from about 2 mm. at the second interspace in the newborn infant to about 9 to 10 mm. at puberty. The thickness of the anterior lamina varies from 0.5 mm. at birth to 2 mm. in later childhood. It is apparent from these figures that unless one is familiar with anatomic relations it would be easy to perforate the sternum.

TECHNIC OF ASPIRATION

The patient should be in the supine position with head slightly extended. This position is facilitated by placing a small pillow under the scapulas. This is especially important in the young infant whose neck is short, for with the head flexed the sternal area may not be readily accessible. Since rapid movement of the chest, or movement of the body generally, makes it difficult to guide the needle carefully in so confined a space, sedation is helpful. A rapidly acting barbiturate is desirable, such as "seconal" (sodium 5-allyl-5-[1-methylbutyl] barbiturate), in doses of 0.003 or 0.006 Gm. (1/20 to 1/10 grains) per pound of body weight, suspended in water and given rectally by catheter. The buttocks are then taped together to prevent expelling the medication. During the average time of fifteen minutes that it takes the drug to act, the skin over the central part of the chest should be prepared with iodine and alcohol. While some workers do not advocate local anesthesia, it is desirable at all ages to relieve the pain of penetrating the periosteum. About 1 to 2 cc. of a 2 per cent solution of procaine is infiltrated intracutaneously over the site to be punctured, and then the subcutaneous tissue and periosteum are infiltrated. One can gage the distance the sternal needle will have to travel from the surface of the skin to the anterior lamina by noting the depth on the shaft of the infiltrating needle when the periosteum is being infiltrated. The local anesthesia is effective in about five minutes; the skin over the sternum is grasped between the thumb and forefinger, and the skin is penetrated in one thrust with the sternal needle. It is then gently pushed through the anterior lamina at a 45 degree angle with the point directed cephalad with a slow boring movement. The anterior lamina is cartilaginous in infants, and the definite give is not elicited as in older children and adults when the anterior plate is penetrated. If one is in doubt as to whether the marrow has been entered it is well to withdraw the stylet and apply suction with a tightly fitting dry 5 cc. syringe. It is always better to stop short of the marrow cavity than to go beyond the posterior lamina and to then retract the needle.

When the marrow cavity has been entered the marrow will bubble slowly into the syringe if suction is sustained. In young infants one may have to be content with the amount that may be collected in the bore of the needle. The amount aspirated will vary from 0.1 cc. to 1 cc., depending on whether the marrow

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5. (*a*) Kato, K.: Sternal Marrow Punctures in Infants and in Children, Am. J. Dis. Child. **54**:209-230 (Aug.) 1937. (*b*) Diwany, M.: Sternal Marrow Puncture in Children, Arch. Dis. Childhood **15**:159-170 (Sept.) 1940.

is being studied directly or by the concentration technic. Aspiration of larger amounts is undesirable because of the possibility of diluting the marrow specimen with sinusoidal blood. Because of the tendency of marrow to clot rapidly the material should be quickly smeared directly on a slide or cover slip or put into a small paraffined tube containing a small amount of dry powdered heparin[6] and gently rotated to prevent coagulation. Heparin is preferable to oxalate, since the latter anticoagulant may produce artefacts in the marrow cells. If smears are made directly they should be thin as the marrow is cellular. The slides are then air-dried and stained with either Wright or May-Grünwald-Giemsa stain for fifteen to twenty minutes.

Many sternal puncture needles have been devised, and each has its proponents. All are essentially similar, with minor modifications, consisting of a strong, short needle (3 to 4 cm. long and about 16 to 18 gage) with a stylet, adjustable guard and a short sharp bevel.

EXAMINATION OF ASPIRATED FLUID

It is not within the scope of this discussion to go into detail about examination of the marrow cells. From a practical consideration certain points should be made. Technical refinements of differential counts of the marrow have been attempted by many hematologists, but for practical purposes they add little to final evaluation of the smear. Primarily one is concerned with a degree of cellularity under standard conditions, gross quantitative variations in cells normally present, especially the myeloid-erythroid ratio and myeloid and erythroblast maturity dispersion, qualitative changes in the cells and the presence of abnormal cells in the smear. Ordinarily, the variations in normal marrow counts are so great that only gross changes are significant. Generally the pathologic bone marrow smears show such striking deviations from the normal findings that a reliable diagnostic impression is possible without a differential count. The sources of error in differential counts of marrow have been discussed elsewhere.[7]

Depending on a variety of variable factors, the total count of nucleated cells of the marrow of normal infants and children will vary from 40,000 to over 1,000,000,[8] and while averages are not warranted on such a small number of cases showing such great variations, one may state that in general infants and children will manifest at least two to three times more nucleated cells than do adults. Before any definite figures can be accepted a large number of cases are needed in which counts are made from marrow obtained under standardized technics. The same criticism is valid for differential counts in which wide varia-

6. Hynsen, Wescott and Dunning.

7. Osgood, E. E., and Seaman, A. J.: Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture, Physiol. Rev. **24**:46-69 (Jan.) 1944. Dinwany.[5b]

8. (*a*) Osgood and Seaman.[7] (*b*) Vogel, P., and Bassen, F. A.: Sternal Marrow of Children in Normal and Pathologic States, Am. J. Dis. Child. **57**:245-268 (Feb.) 1939. (*c*) Diwany.[5b] (*d*) Scott, R. B.: Sternal Puncture in Diagnosis of Diseases of Blood-Forming Organs, Quart. J. Med. **8**:127-172 (April) 1939.

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tions within the same age groups are observed. Until more accurate data are obtainable on a larger number of children only general figures can be stated.

The erythroid elements more closely approximate the myeloid cells in the marrow of infants. The myeloid-erythroid ratio increases from a figure of 1.9 in infancy to 2.4 at 4 years of age and 3.4 at puberty.[9] Significant general trends of this type are important as a decreased myeloid-erythroid ratio would indicate predominant erythropoietic activity, whereas an increased myeloid-erythroid ratio would suggest increased leukopoietic reaction. The distribution of the various cells in differential counts can be expressed only in ranges until a sufficiently large number of normal subjects are studied in each age period under standardized conditions. The following ranges of various cell types have been seen in infants and children, and it should be noted that they do not differ very much from adult values.[8d]

Ranges of Various Cell Types.

	Children (All Ages) Per Cent	Adults Per Cent
Myeloblasts or leukoblasts, Premyeloblasts	2—8	1—5
Myelocytes	10—25	10—25
Metamyelocytes	8—40	20—45
Mature neutrophils	10—35	5—25
Eosinophils	1.5—6	0.5—9
Lymphocytes	4—35	2—25
Monocytes	0.0—5	0.0—9
Nucleated erythroid cells	11—40	10—30
*Megakaryocytes	0.06—0.5	0.06—.05

*Megakaryocytes should not be included in the differential count of other cells as their distribution in the smear is irregular in aspirated material. They should be counted separately under low power.

The maturity dispersion of erythropoietic cells of the marrow range from: proerythroblast 3 to 5 per cent, erythroblasts or basophilic normoblasts 10 to 20 per cent, polychromatic and orthochromatic normoblasts 75 to 85 per cent. True megaloblasts are not seen in the normal marrow although workers of different schools of hematology would not agree with this statement.

Megakaryocytes, mostly of the adult type, are irregularly scattered throughout the smear and tend to accumulate at the edges and at the end of the smear. Lymphocytes, or cells resembling them, are relatively frequent in children's marrow. These cells are smaller than the usual lymphocyte and have dense nuclei and relatively little cytoplasm. They have been referred to as hematogones and may not be identical with the small lymphocytes found in the circulating blood. Typical lymphocytes of the medium and large variety are seldom seen in the bone marrow and when present probably are due to unavoidable dilution with sinusoidal blood. The same is true for the monocyte.

INDICATIONS FOR STUDY OF BONE MARROW

The value of studies of the bone marrow may be considered under the following groupings:

9. Kato,[5a] Osgood and Seaman,[7] Vogel and Bassen,[8b] Diwany.[8b]

1. Obscure conditions presenting anemia, leukopenia and thrombocytopenia.
2. As a corroborative diagnostic procedure and to facilitate the prognosis and treatment of hematologic disorders.
3. As an aid in ruling out disorders of the blood-forming organs from diagnostic consideration (negative value).
4. As a confirmatory diagnostic aid in malignant tumors when direct evidence of metastasis may be found in the sternal marrow.
5. As a method of demonstrating the characteristic lipid-containing histiocytes of the diseases of lipid metabolism, such as Gaucher's, Niemann-Pick and xanthomatosis.
6. As a complementary procedure in certain protozoal and fungus diseases when examination of the peripheral blood is not diagnostic (malaria, leishmaniasis, histoplasmosis).

CHANGES IN THE BONE MARROW IN VARIOUS PATHOLOGIC STATES

I. THE ANEMIAS

(1) *Hemolytic Disease of the Newborn.*—Hemolytic disease of the newborn or erythroblastosis fetalis may be adequately diagnosed without study of the bone marrow. While the marrow generally shows a marked increase in erythropoiesis (this is roughly proportional to the severity of the anemia) there may be some disparity between peripheral blood and bone marrow findings because of extensive extramedullary erythropoiesis in the liver, spleen and other ectopic sites. The erythroid maturity dispersion is toward the immature level although some cases merely show hyperplasia at the normoblastic level. More data on the bone marrow in different types and a larger number of cases are needed before an intelligent evaluation of marrow findings in this disorder may be presented.

(2) *Megaloblastic Anemia of Infancy and Childhood.*—The marrow findings in megaloblastic anemia of infancy described by Dr. Zuelzer are characteristic and diagnostic. True pernicious anemia is rare at this age period, and the presence of true immature megaloblasts, pathologic granulopoiesis and reduction in megakaryocytes in the marrow associated with macrocytic anemia, leukopenia and thrombopenia in the peripheral blood is characteristic. Bone marrow studies in this condition are both diagnostic and useful as a guide for treatment. Administration of folic acid effects changes in the marrow within twenty-four hours, whereas the peripheral blood may not show evidence of successful therapy for days.

If true pernicious anemia should occur in childhood, the findings and therapeutic response are the same, but unless therapy is maintained relapses will occur, because this type of anemia is on a constitutional basis. This is not true of the megaloblastic anemia in infancy described by Zuelzer and Ogden.[10]

10. Zuelzer, W. W., and Ogden, F. N.: Megaloblastic Anemia in Infancy: A Common Syndrome Responding Specifically to Folic Acid Therapy, Am. J. Dis. Child. **71**:211-243 (March) 1946.

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Macrocytic anemia with a megaloblastic type of bone marrow may also be associated with other diseases in which there is a deficiency of liver complex or of folic acid, like sprue or some cases of celiac syndrome. Other examples are nutritional macrocytic anemia and some cases of organic disease of the alimentary tract. Conversion of the megaloblastic marrow by folic acid and liver extract is similar to that observed in pernicious anemia. Clinical and laboratory findings must therefore be evaluated with the bone marrow study. Macrocytic anemias are not always associated with a megaloblastic marrow. Some patients with aplastic anemia, hemolytic anemia (Lederer's), leukemia and cirrhosis of the liver may have a macrocytic anemia with a normoblastic bone marrow, and these patients do not respond to folic acid or to the specific principle in liver extract. The presence of true megaloblasts in the bone marrow is a good index that a patient with macrocytic anemia will respond to folic acid or liver extract.

The problem of morphologic identification of a true megaloblast is therefore more than an academic question to be debated by various schools of hematology. Since the discovery of liver extract and more recently folic acid it has become increasingly apparent that more precise knowledge of the pathologic process in certain marcrocytic anemias and successful treatment depend on positive identification of the megaloblast. The point of view taken in this discussion is that the presence of the true immature megaloblast indicates a dysplastic type of erythropoiesis, and that these cells do not give rise to normoblasts or mature normocytes. Further evidence for this opinion may be found elsewhere.[11]

(3) *Iron Deficiency or Microcytic Hypochromic Anemias.*—Bone marrow studies in this type of anemia are informative but not diagnostic. In the untreated iron deficiency state the bone marrow shows a normoblastic hyperplasia consisting predominantly of small, mature, polychromatic normoblasts. The myeloid cells are not significantly changed unless toxic or infectious factors are present. Successful therapy with iron returns the bone marrow to normal and restores normal size and hemoglobin content to the circulating erythocytes.

(4) *Hemolytic Anemias.*—Familial hemolytic icterus is a characteristic example of this group. The bone marrow in this disease shows a marked normoblastic hyperplasia. The marrow study is not as diagnostic as the clinical and laboratory findings. Other hemolytic anemias show similar findings (sickle cell, acquired hemolytic states, etc.).

(5) *Aplastic Anemia or Panmyelophthisis.*—The terminology of this type of anemia would presume knowledge of the state of the bone marrow. While the diagnosis often can be postulated on the basis of study of the peripheral blood, study of the bone marrow is essential for

11. Jones, O. P., and Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2068.

verification. Acute leukemia in the aleukemic phase and agranulocytosis may be confused with aplastic anemia unless the bone marrow is studied. Pronounced hypoplasia of all cellular elements of the marrow in aplastic anemia is reflected by anemia, leukopenia and thrombocytopenia in the peripheral blood. Patients with chronic panmyelophthisis may show a moderate cellularity early in the course of the disease, when remissions may occur. These patients often have a peculiar type of erythropoiesis characterized by macrocytic anemia with giant normoblasts in the bone marrow. Relapses are associated with a decrease in this type of erythropoiesis whereas remissions are associated with increased numbers of the giant-sized normoblasts. This is not a specific finding, however, as similar changes in the bone marrow are seen in cirrhosis of the liver.

(6) *Anemia Associated with Chronic Infection, Malignant Disease and Chronic Nephritis.*—The bone marrow in these conditions is characterized by a depression of erythropoiesis. This emphasizes the futility of iron therapy and the importance of supportive therapy with blood transfusions. The type of anemia is usually normocytic.

II. LYMPHADENOPATHY AND ENLARGEMENT OF THE SPLEEN

Patients exhibiting enlarged lymph nodes and spleen raise the question of diseases of the blood-forming organs in which study of the bone marrow is of positive or negative diagnostic value. The bone marrow in most acute and chronic infections associated with lymphadenopathy and splenomegaly usually shows a myeloid hyperplasia with a toxic type of granulopoiesis which is not specific.

In Hodgkin's disease, the marrow is not diagnostic but usually shows a variable degree of hyperplasia. The hyperplasia may involve the megakaryocytes, plasma cells, histiocytes or reticulum cells. A shift to the left of granulopoiesis is found more often, but the changes in the bone marrow are as nonspecific and as variable as those of peripheral blood. The characteristic pleomorphic histology of Hodgkin's disease can be demonstrated only by biopsy of lymph nodes.

Chronic leukemia (myeloid or lymphatic) is not common in infants and children, and the peripheral blood changes are characteristic when the disease is present. Sternal aspiration is therefore of value for purposes of corroboration. Early in the disease acute leukemia is a difficult diagnostic problem in infants and children. A great many cases would certainly be overlooked if the bone marrow were not investigated, since the peripheral blood in some cases may reveal few abnormal cells. Low white counts are common, and it is only after diligent search by an experienced observer that the normal cells may be found. Many cases of supposed agranulocytosis, thrombocytopenic purpura or aplastic anemia in children turn out to be acute leukemia on careful study of the bone marrow. Children with anemia, leukopenia and thrombocytopenia should

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be subjected to sternal aspiration, as the bone marrow findings are of great value in differential diagnosis. I should like to reemphasize the point that Dr. Zuelzer made in his discussion, namely, that the immature cells in acute leukemia are pathologic cells and should not be compared with normal primitive cells (myeloblasts and lymphoblasts) because of mere resemblance. It is of doubtful value hematologically and clinically, therefore, to attempt to distinguish between acute myelogenous or lymphatic leukemia on the basis of present knowledge of the morphologic, clinical or etiologic criteria.

The bone marrow findings in infectious mononucleosis may be of interest, apart from the aid given by the clinical findings, absence of anemia, positive heterophil agglutination and peripheral blood findings. In spite of the large number of atypical lymphocytes in the peripheral blood the bone marrow is not so involved, but instead shows a myeloid hyperplasia.[12] In cases of acute infectious lymphocytosis, especially those with high counts, differential diagnosis may be necessary between this condition and chronic lymphatic leukemia. The bone marrow in acute infectious lymphocytosis lacks any evidence of infiltration with lymphocytes, and in a few cases which we have studied the changes in the bone marrow were not unlike those of infectious mononucleosis. Sternal aspiration is, therefore, another aid in differentiating benign lymphocytosis from leukemia.

Banti's syndrome, caused by thrombophlebitis of the mesenteric or splenic vein, may be present in childhood. In those cases in which cirrhosis of the liver is not marked or of long standing the bone marrow may exhibit myeloid hyperplasia with arrest of maturation of the myeloid and megakaryocytic elements. The peripheral blood findings reflect the changes in the marrow with a moderate anemia, leukopenia and thrombocytopenia. Splenectomy performed at this stage will often restore the blood to normal. If, however, the syndrome results from obstruction of the portal vein and early portal hypertension, advanced cirrhosis is usually present, and the bone marrow will show evidence of marked erythroid immaturity in addition to myeloid hyperplasia and arrest of maturation. In such cases splenectomy[13] is not beneficial.

Children with Still's disease manifest changes in the bone marrow similar to those described for thrombophlebitis of the splenic vein.

In patients with splenic neutropenia or pancytopenia the bone marrow reveals varying degrees of hyperplasia involving the granulopoietic or erythropoietic cells with arrest of maturation. Splenectomy often results in improvement theoretically by removing the splenic hormonal fac-

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12. Limarzi, L. R.; Paul, J. T., and Poncher, H. G.: Blood Marrow in Infectious Mononucleosis, J. Lab. & Clin. Med. **31**:1079-1100 (Oct.) 1946.

13. Limarzi, L. R.; Jones, R. M.; Paul, J. T., and Poncher, H. G.: Sternal Marrow in Banti's Syndrome and Other Splenomegalic States: Effect of Splenectomy, Am. J. Clin. Path. **13**:231-248 (May) 1943.

tor which inhibits the maturation and delivery of cells to the peripheral blood.

Study of the bone marrow may be of value in the differentiation of polycythemia vera (which is rare in children) from secondary polycythemia. In symptomatic polycythemia the marrow findings may be normal or show a moderate erythroid hyperplasia whereas in polycythemia vera hyperplasia of all marrow elements is found.

Diseases of lipid metabolism with enlarged spleen and lymph glands may be diagnosed occasionally by the finding of the characteristic cells on sternal aspiration. Typical lipid-containing histiocytes of xanthomatosis, Gaucher's and Niemann-Pick disease have been found in the marrow but splenic puncture is a more certain diagnostic procedure in the last two diseases. We have encountered known cases of advanced essential xanthomatosis in which the long bones were extensively involved and yet we were unable to demonstrate xanthoma cells in the sternal marrow.

III. TUMORS

The changes in the bone marrow in myelomatosis are characteristic. Myeloma cells are large round or ovoid cells, often with an eccentric nucleus of large size. The cytoplasm is deeply basophilic, and occasionally a pale perinuclear zone is present. Vacuoles in the cytoplasm are frequent. The number of myeloma cells observed is usually adequate to make the diagnosis certain. We have not encountered multiple myeloma in the children we have studied.

Occasionally one is able to demonstrate cells of neuroblastoma and other malignant tumors in the sternal marrow, but the finding is usually inconstant and occurs late in the disease after metastasis has occurred.

IV. PURPURA AND HEMORRHAGIC DISORDERS

Sternal marrow studies are of great value in the differentiation of essential thrombocytopenic purpura (Werlhof's disease) from symptomatic thrombocytopenic purpura. The primary or essential type is associated with a definite megakaryocytic hyperplasia. Splenectomy performed with such a marrow pattern is usually successful whereas a decrease in megakaryocytes is a definite contraindication to splenectomy. The bone marrow in symptomatic thrombocytopenic purpura and nonthrombocytopenic purpuras show no characteristic marrow pattern. In hemophilia the megakaryocytes are quantitatively and morphologically normal.[14]

V. AGRANULOCYTOSIS AND GRANULOCYTOPENIA

The bone marrow has important prognostic value in the investigation of neutropenic states due to drugs (such as sulfonamide compounds, aminopyrine and thiouracil) and infection. If the granulopoietic tissue

14. Limarzi, L. R.; Poncher, H. G., and Birch, C. L.: The Bone Marrow in Hemophilia During Life: A Study of the Cellular Elements and the Coagulation Time of the Marrow Blood, J. Lab. & Clin. Med. **31**:777-784 (July) 1946.

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in the marrow is reduced or depleted and the erythroid tissue is hypoplastic the prognosis will usually be poor in spite of therapy. However, some patients with leukopenia and granulocytopenia may actually show hyperplasia of the myeloid tissue with arrest of maturation at a relatively mature level. In this type of case prognosis for recovery is usually good. The use of sternal aspiration for the differentiation of apparent neutropenic states of acute leukemia and true agranulocytosis has been previously discussed.

VI. PROTOZOAL AND FUNGUS DISEASES

We have not had extensive experience with malaria or leishmaniasis, but the value of sternal aspiration was first established in these diseases. Sternal puncture may reveal the parasites when they cannot be found in the peripheral blood. We have been able to confirm the diagnosis of histoplasmosis of Darling by sternal aspiration but our experience is not sufficiently extensive to assess its diagnostic value in a large group of cases.

SUMMARY AND CONCLUSIONS

The technic and diagnostic application of sternal puncture have been described.

The use of this procedure has added to the knowledge of the pathogenesis of many disorders of hematopoiesis which were imperfectly understood by studying the peripheral blood alone.

Sternal puncture is of diagnostic value in the leukemias, megaloblastic anemia of infancy, myelomatosis, malaria, leishmaniasis, in some cases of Gaucher's and Niemann-Pick disease, xanthomatosis, metastatic tumors such as neuroblastoma and lymphosarcoma.

Sternal puncture is of confirmatory or prognostic value in the study of the anemias of infancy and childhood, granulocytopenia, purpuric states, thrombophlebitis of the splenic vein and splenic pancytopenia.

Study of the bone marrow is an extension of hematologic investigation and should not replace careful history taking, physical examination and complete laboratory study.

The negative value of sternal puncture in practice is important because it permits the physician to speak with assurance about the presence or absence of certain diseases which he must consider in differential diagnosis.

Finally, the technic of sternal aspiration may be mastered by any qualified physician who has acquainted himself with the anatomy of the sternum in infants and children and the technical details of the procedure. The correct preparation and interpretation of the aspirated material is important, for much of the diagnostic value of study of the marrow may be lost or an erroneous diagnosis may be made if interpretation is attempted by a person with inadequate training in hematology.

GARGOYLISM

II. Study of Pathologic Lesions and Clinical Review of Twelve Cases

STUART LINDSAY, M.D.
WILLIAM ANTHONY REILLY, M.D.
THELMA J. GOTHAM
AND
RICHARD SKAHEN, M.D.
SAN FRANCISCO

GARGOYLISM (Hurler's syndrome, lipochondrodystrophy and dysostosis multiplex) is a rare disease of early childhood, characterized by a gruesome facies, skeletal deformities, cloudy corneas, mental deficiency, retarded skeletal growth, hepatosplenomegaly, umbilical hernia and hirsutism. Death usually occurs by the end of the first decade. About 107 cases have been reported and collected to date.[1]

The etiologic basis of the process has remained obscure. While it was apparent that the cells of certain tissues are distended with some stored material, neither chemical nor histochemical technics consistently showed the composition of this substance. The widespread nature of the storage phenomenon was not appreciated; furthermore, it was not generally recognized that the striking skeletal alterations are the result of storage of a substance in the cytoplasm of most of the skeletal cells.

Few autopsy reports have appeared; while many of the lesions were described, further examination of all tissues appeared warranted. In our own experience, study of the pathologic changes of the first few fatal cases in 1942 immediately suggested that the fundamental alteration of the tissues was storage of a water-soluble substance, possibly a complex carbodydrate, but not a lipid or a protein material. Further observations strengthened this hypothesis. It is shown in the present report that the altered tissue cells store material giving the histochemical staining reactions for glycogen and glycoprotein. In addition, studies on rabbit tissues following injection with methyl cellulose, a macromolecular carbo-

From the Departments of Pathology and Pediatrics, University of California Medical School.

1. Reilly, W. A., and Lindsay, S.: Gargoylism (Lipochondrodystrophy): I. Review of the Clinical Findings in Eighteen Cases, Am. J. Dis. Child. 75:595 (April) 1948.

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hydrate, are cited in this paper and have revealed histologic and gross lesions reproducing some of the lesions of gargoylism.[2]

In this paper, we present the clinical and pathologic observations at autopsy in 8 cases and the clinical and surgical pathologic findings in 4 additional cases. Carbohydrate storage in and the physiologic aspects of the disease will be pointed out, and the relation to carbohydrate and other macromolecular storage diseases will be discussed.

REPORT OF CASES

CASE 1.—*Clinical History.*— W. W., a 6½ year old white boy, entered the University of California Clinic in August 1930 because of hearing and speech deficiencies. A younger brother (case 12) had gargoylism, and both patients have been reported on previously.[3]

In the present patient, the onset of diarrhea, fever and vomiting occurred at the age of 6 months. The stools occasionally contained blood. The diarrhea continued throughout life, although it became less severe in later years. The patient's abdomen became decidedly protuberant, and an umbilical hernia appeared when he was 1 year of age. In spite of many physical disabilities, he had normal mentality. He learned to read lips without instruction and to convey his thoughts by actions and limited speech. His voice was husky and nonresonant. His tonsils and adenoids were removed in his second and fourth years, respectively, because of frequent infections of the respiratory tract. The infections were accompanied with enlarged, tender cervical lymph nodes which caused pain on eating. Otalgia and otorrhea were not present. He had occasional productive cough and infrequent dyspnea. There was no history of rheumatism or chorea. From the age of 3 to 4½ years, he had been given thyroid extract without benefit.

Physical examination on his admission to the clinic showed that the boy had the typical facies of gargoylism, though the corneas were not cloudy. The skin was thickened, coarse and adherent, especially over the dorsal surfaces of the hands, which were clawed. His height was 110 cm. He had a dolichocephalic skull. In the axillas and on the extensor surfaces of the arms were noted numerous, elevated, round nodules which were firm, nontender, circumscribed and discrete. His hearing was extremely deficient. Otologists were unable to determine whether the deafness was congenital or acquired. The heart was normal except for a transient systolic murmur. The lungs, blood vessels, pulse rate and blood pressure were normal. The abdomen was enlarged. The edge of the liver extended 8 cm. below the right costal margin, and the spleen extended 15 cm. below the left costal margin. Both organs were smooth, firm and nontender.

Laboratory Examination: Results of blood studies were normal, though the white blood cell count ranged in the lower limits of normal. No esoinophilic granulations were seen in the white blood cells. The amount of serum calcium and the results of dextrose tolerance test, urinalysis and examination of stools were normal. The Kolmer tests on the blood and spinal fluid and the tuberculin test gave negative reactions. The basal metabolic rate was +12 per cent. A biopsy specimen of the skin showed subcutaneous fibrosis.

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2. Lindsay, S.: Unpublished data.

3. Reilly, W. A.: An Atypical Familial Endocrinopathy in Males with a Syndrome of Other Defects, Endocrinology **19**:639, 1935.

During October 1931, after an attack of measles, his hearing improved temporarily, and he was able to speak a few words. The skin had fewer infiltrations. During this interval he had received some thyroid extract and had grown 2.0 cm. in length. The nasal margins of the optic disks were slightly blurred. The total cholesterol of the blood was 162 mg. per hundred cubic centimeters. A moderate leukopenia (5,400 cells) was present. Roentgenographic examination of the skeleton at the age of 8 years 3 months in April 1932 showed his bone age to be between 5 and 7 years. By September 1932, after attending a school for the deaf for one and a half years, he showed progress with words and sign language, but his hearing was entirely gone. He had grown only 7.5 cm. after use of thyroid extract for twenty-five months. Treatment with thyroxin U.S.P. (0.8 mg. orally daily) was started. At this time the retina showed white streaks, which were interpreted as remains of the covering of the nerve sheath. The optic nerves were blurred, but no cloudiness of the corneas was noted. Gastric analysis gave normal results.

After discontinuance of thyroxin for one week, a normal calcium balance existed as shown by the Aub test. The basal metabolic rate was +8.6 per cent.

In November 1932 the clinical impression of bilateral coxa vara was confirmed on roentgenograms. The metacarpals and carpals were wide, and the epiphysial age was retarded more than two years. His intelligence quotient at this time was 117; it never was reduced below normal. He had grown only 10 cm. in the three years of thyroid therapy. He had acquired some speech. The left optic disk was more edematous at this time. Occasionally, he had mild dyspnea, but his heart was normal on examination except for the systolic murmur. Despite the absence of visible kyphosis, roentgenograms showed a narrowing of the first lumbar vertebra.

On Nov. 15, 1933, he died suddenly during an episode of pulmonary edema. His age at death was approximately 10 years.

Gross Description.—The autopsy was performed twenty-four hours after death by Dr. Charles Rosson. The heart weighed 190 Gm. The left ventricle measured 1.5 cm. in thickness and the right ventricle 0.5 cm. The valves measured as follows: aortic, 4 cm.; pulmonary, 3.5 cm.; tricuspid, 8 cm., and mitral, 1.5 cm. They were normal except for the mitral valve, which was stenotic and showed fibrous thickening and small, discrete translucent nodules along its free edge. The right ventricle and auricle were moderately dilated. The pericardium, myocardium and endocardium showed no alteration. Three, small, elevated, intimal plaques were noted in the aorta just distal to the aortic valve. The right lung weighed 250 Gm. and the left lung 240 Gm. Both lungs were congested and moderately edematous. Numerous lobules beneath the pleural surface were atelectatic. The pleural and pericardial cavities were normal. The hilar lymph nodes were slightly enlarged. The thymus gland appeared enlarged, weighed 65 Gm. and extended well down over the auricular portions of the heart. Its parenchyma was normal on section. The edge of the liver extended 10 cm. below the right costal margin and the xiphoid process. The liver weighed 2,500 Gm. The anterior border was rounded. The parenchyma was soft and pale and had a nutmeg appearance. The spleen was large and weighed 590 Gm.; it filled the upper left quadrant of the abdomen and was extremely soft. Its capsule was tense. On the cut surface were large, pale lymphoid follicles surrounded with a reddish yellow, soft, hyperplastic pulp. The spleen measured 18 cm. in length. The pancreas weighed 100 Gm., and postmortem necrosis was evident. The gallbladder and gastroenteric tract were normal. Each kidney weighed 110 Gm. The capsules stripped easily. The cortex averaged 0.4 cm. in thickness and was pale, but it was well demarcated from the medulla. The pelves, ureters, bladder and prostate gland showed nothing ab-

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normal. The left adrenal gland weighed 4.5 Gm. and the right adrenal gland 5 Gm.; both were normal. The thyroid gland and testes were normal. Inspection of the cranial cavity showed no alteration. The sella turcica was not enlarged, and the pituitary gland was of normal size. The brain weighed 1,700 Gm. and showed no abnormalities externally or on section.

Microscopic Description.—Lymphocytic infiltration of the pericardial fat was minimal. The endocardium of one papillary muscle of the left ventricle was widened and consisted of broad, hyalinized, collagenous fibers (fig. 1). The connective tissue cells between the fibers had abundant cytoplasm with a pale, bluish gray, granular-vesicular appearance. The cytoplasm was distinctly outlined, and the cells and nuclei were oval or round rather than spindle shaped. Visible between some collagenous fibers were elongated masses of similar cytoplasm without

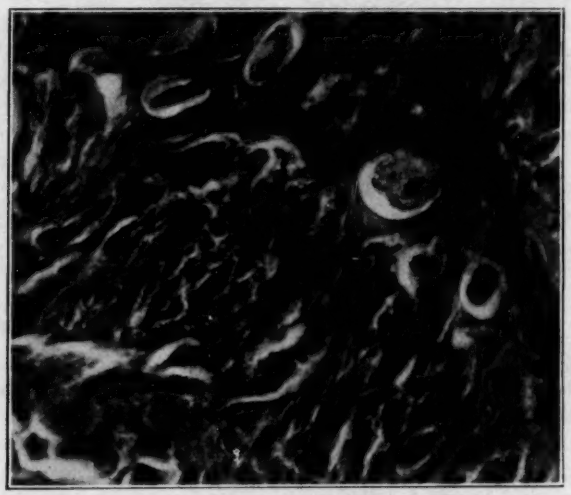

Fig. 1.—Photomicrograph showing broad, hyalinized, collagenous fibers of endocardium of papillary muscle of left ventricle (case 1); hematoxylin and eosin; × 500.

visible nuclear structures. A similar fibrous thickening was present at the point of attachment of the aortic valve cusps. This altered connective tissue extended a short distance into the adjacent myocardium where it replaced groups of muscle fibers. Elsewhere the endocardium, myocardium and interstitial tissues were entirely normal. The coronary vascular system showed no alteration.

The intima of the first portion of the aorta was widened at the site of the grossly visible plaques. The intima was composed of fibrillary connective tissue without the cellular alterations seen in the endocardium at the base of the aortic valve. The aortic media contained a few scattered lymphocytes, mainly in a perivascular situation.

Vascular congestion of the lungs was moderate, and in the alveoli were many macrophages with greatly vacuolated cytoplasm. Other macrophages contained a small amount of golden pigment.

The hepatic lobules were more distinctly outlined than normal. Their outlines were irregular, and they tended to be separated from each other by narrow, fibrous septums. The hepatic parenchymal cells, which did not lie in the usual

cord arrangement, were greatly altered. The cells were large and had distinct nuclear membranes, and the nuclei were eccentrically placed. The cytoplasm was abundant, granular, eosinophilic and distinctly vesicular. The sinusoids in the central portions of the lobules were congested.

The splenic capsule and the trabeculae were normal. The lymphoid follicles appeared smaller and fewer in number than normal for the age. The central arterial vessels showed no alteration. The splenic sinusoids were wide and contained many neutrophilic and eosinophilic leukocytes, with fewer plasma cells and large mononuclear cells. These mononuclear cells, as well as many of the reticuloendothelial cells lining the sinusoids, showed a distinct but mild vacuolization of their cytoplasm.

Postmortem necrosis of the pancreatic parenchyma was evident. An occasional medium-sized pancreatic artery had a thickened intima consisting of hyalinized connective tissue with altered fibrocytic cells, the cytoplasm of which was distended, granular and vesicular.

The renal glomeruli were unusually large and almost completely filled the glomerular spaces. There were increased numbers of both epithelial and endothelial cells in the glomerular tufts, associated with almost complete obliteration of the capillary channels and thickening and fraying of the basement membranes of the tufts. A few desquamated epithelial cells and neutrophilic leukocytes lay in the glomerular spaces. The epithelial cells lining the glomerular spaces were occasionally enlarged and swollen. The cytoplasm of the cells lining the convoluted tubules was so abundant and granular as to produce almost complete obstruction of the lumens. A few nuclei of these cells were degenerating or absent. Except for a minimal lymphocytic infiltration, the pelvic tissues were normal.

The testicular tubules were small and immature. Many tubules contained enlarged cells, four to five times the size of adjacent cells, which had nuclei with a fine chromatin network and a single eosinophilic nucleolus. The cytoplasm of these enlarged cells was granular, abundant and eosinophilic. A remarkable alteration in the interstitial tissue had occurred, associated with cellular enlargement and clear cytoplasmic swelling. While no alteration in the epithelium of the epididymis or vas deferens was seen, the connective tissue in each of these structures was composed of fibroblastic cells with abundant, clear cytoplasm.

The skin showed no histologic changes. No alteration in the pituitary or adrenal glands was noted. The thymic lobules were large and consisted mainly of lymphocytes, with smaller numbers of reticular cells and a few scattered Hassall corpuscles. The lobules were separated by wide zones of edematous connective tissue.

A section from a costochondral junction showed the erythropoietic foci to be larger than normal, and many of the nucleated red blood cells were less mature than normoblasts. The cells of the myeloid and megakaryocytic series were present in normal numbers. In the rib the cortical layer and the trabeculae of the marrow were unusually thin. Alteration in the osteocytes within them was not significant. The epiphysial line revealed no evidence of growth. The cartilage cells were unusually large and almost completely filled the lacunar spaces in the cartilaginous matrix. The cytoplasm of the cartilage cells was more abundant than usual and was granular and vesicular. Some of the connective tissue cells in the outer layer of the periosteum showed similar alteration: the cytoplasm was abundant, finely vacuolated and granular.

In the central nervous system, the cerebellar tissues were not altered. Some of the connective tissue cells in the arachnoid were enlarged and showed the same changes in the cytoplasm as described elsewhere. The degree of cerebral edema was

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great. The nerve cells of the cerebral cortex did not show the enlargement seen in other cases of this disease. However, about the blood vessels in the white matter of the cerebral hemispheres were groups of enlarged fibroblastic connective tissue cells with abundant, finely granular cytoplasm. No formation of perivascular cysts was evident.

CASE 2.—*Clinical History.*—G. N., an Armenian girl, was observed in the University of California Clinic from birth, Sept. 20, 1928, until death, March 28, 1936.

The patient was a full-term twin girl. The development of her twin sister was normal and without evidence of gargoylism, and she is now 19 years of age. The placenta was distinctly divided, suggesting a double ovum pregnancy, though microscopic examination was not made. Subsequently, another sister with gargoylism was born in this family (case 11). At birth, a large umbilical hernia was noted. Lumbar kyphosis appeared at 6 months; at 1½ years hirsutism on the back was noted. The joints failed to extend fully, and the hands were clawed. At 20 months of age she was dwarfed and could not walk, talk or stand by herself. Her mental development was retarded, and the head was abnormally large. Hepatosplenomegaly had appeared. Corneal cloudiness developed at the age of 3 years. With the slit lamp, the deeper layers of the corneas contained many punctate, highly refractile dots. The interpupillary distance was unusually wide, and moderate exophthalmos and an alternating convergent squint were present. The ocular tension was normal. An encephalogram made at 4 years of age showed uniform dilation of the ventricles.

In October 1934, at the age of 6 years, the patient measured only 91 cm. in height. The head was large with occipital and parietal flattening. The expression was dull and stupid. The nose was saddle-shaped with widened nares, and nasal obstruction was severe. The mandible was smaller than normal and misshapen. The condyles were rudimentary. The teeth were peg shaped and asymmetric in size and shape. The hearing seemed to be impaired. Sprengel's deformity of the scapulas was present. Associated with the kyphosis was left lumbar scoliosis. Decided flaring of the lower costal margins was noted. The abdomen was protruding, and a large umbilical hernia was present. The patient was unable to stand unassisted and could utter only unintelligible sounds. The corneal opacity and the exophthalmos had progressed.

Laboratory Examination: Pronounced eosinophilic granulation of the neutrophilic leukocytes was observed in the blood film. This change was present in none of the cells aspirated from the bone marrow or spleen. Results of the oral dextrose tolerance test were normal. The urine was normal. Chemical examination of the blood showed 93.9 mg. of total cholesterol, 12 mg. of calcium and 4.1 mg. of phosphorus per hundred cubic centimeters. The reaction to the Kolmer test of the spinal fluid was negative. Intravenous pyelograms revealed nothing abnormal.

When the patient was 6 years of age, a biopsy specimen of the spleen was obtained. No alteration in the capsule or trabeculae was seen. The few lymphoid follicles were small. The reticuloendothelial cells lining the sinusoids and lying between them were enlarged and had clear, vesicular cytoplasm. Normal numbers of red and white blood cells were present in the splenic pulp.

Gross Description.—(No tissues or slides of this case were available for study by us. The following report is a summary of the autopsy record from the Sonoma State Home, Eldridge, Calif.)

The autopsy was performed fifty-six and a half hours after death by Dr. Frank A. Mayner. The body measured 91 cm. in length. The face had a mon-

goloid appearance with moderate exophthalmos. The eyelids were edematous. The nasal bones were depressed. The thorax was shortened, and the ribs appeared unusually close together. The abdomen was greatly distended, owing mainly to distention of the stomach and bowel by air. The left pleural cavity contained approximately 200 cc. of clear, pale fluid, but the right pleural cavity was normal. The thymus gland had but one lobe, which lay in the anterior mediastinum. The pericardium was normal. The heart weighed 180 Gm. and had a normal appearance throughout except for the mitral and tricuspid valves. Along the free edge of these valves were numerous coalescing nodules averaging 0.2 cm. in diameter. Each lung weighed 150 Gm. Moderate congestion was noted, particularly in the posterior portions of the lungs. The apex of the left lung was atelectatic. A primary tuberculous focus was present in the upper lobe of the left lung, and numerous calcified lymph nodes were present in the left mediastinum. The liver weighed 550 Gm. It had a smooth surface. The cut surface presented a firm, yellowish brown parenchyma with distinct lobular markings. The gallbladder and extrahepatic bile ducts were normal. The spleen weighed 125 Gm. The pulp was firm and reddish brown, and the malpighian bodies were not visible. The gastroenteric tract was normal throughout except for a submucous lipoma near the pyloric end of the stomach. The pancreas was normal. Each kidney weighed 75 Gm. The capsules stripped easily. The cortices and medullas were well demarcated. The renal pelves, the ureters and the bladder were normal. The adrenal glands were normal in size, shape and appearance. No alteration in the layers of the aorta was seen. The internal genitalia were not altered.

The skull was normal except for enlargement. The meninges, especially over the frontal lobes, were thickened and grayish. The cerebral convolutions were moderately flattened. The sella turcica was enlarged and deepened, although it contained a gland of normal size and shape. The ventricular system of the brain was not enlarged. Numerous tiny cystic cavities were scattered throughout the white matter of the cerebral hemispheres and also were present in the region of the dentate nuclei and in the white matter of the cerebellum. In the left internal capsule was a similar but larger cyst measuring 1 by 1 by 0.5 cm.

Microscopic Examination.—The myocardial, epicardial and endocardial layers of the heart were normal. The pronounced thickening of the mitral valve was due to whorl-like strands of edematous fibrous tissue surrounding enlarged, swollen fibroblastic cells. This tissue had the appearance of fibrocartilage. Many of the small bronchi and adjacent alveoli contained purulent exudate. All the hepatic cells were distended and vacuolated. The central portions of the lobules were moderately congested.

The spleen, pancreas and adrenal glands presented a normal histologic appearance. No alteration in the thyroid or pineal glands was seen.

The renal capsules showed a slight fibrous thickening. Capsular thickening of the glomeruli, with proliferative epithelial changes producing typical crescents was observed. The interstitial tissue showed fibrous thickening and was moderately infiltrated with lymphocytes. No tubular alteration had occurred.

The cysts in the left internal capsule, as well as those in the cerebral hemispheres and dentate nuclei of the cerebellum, represented widened perivascular spaces containing numerous phagocytic cells surrounded with edematous glial elements. The myelin sheaths of the cervical cord and medulla showed no degeneration. Alteration in the cerebral nerve cells was not described. Fibrous thickening and edema of the cerebral arachnoid was noted.

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CASE 3.—*Clinical History.*—J. P., a 5 year old boy, born July 8, 1935, was admitted to the University of California Clinic on Oct. 3, 1940.

The family history disclosed that a younger brother (case 4) also had gargoylism.

The patient appeared normal at birth. The teeth began to erupt at between 6 and 7 months of age. The boy walked at 19 to 20 months. Hearing was normal until 2 years of age, and at that time deafness became progressive. The boy spoke in monosyllables at 14 to 16 months, but by the time of entry to the clinic he did not talk, although he could indicate his wants by gestures.

The first signs of gargoylism appeared at the age of 5 months, when kyphosis in the lumbar region developed. At 1½ years of age his facial appearance began to change. The head assumed a peculiar shape; the lower jaw became enlarged, and the tongue thickened. The abdomen became protuberant, and an umbilical hernia developed. The hands became enlarged, and the ankles thickened. An abnormal distribution of fat was also noted. Height or weight had not increased during the two years before entry. The skin had become thickened and puffy.

On his entry to the clinic, his height was 85 cm. His appearance was typical of gargoylism. The head was large and scaphocephalic, with prominent frontal bosses. The orbits were widely separated and the eyes large. He had a typical saddle nose with flaring nares. The mandible was broad and the lips somewhat thickened. The tongue was large. The teeth were small and widely separated. The skin was coarse and granular, and over the back, buttocks, abdomen and neck were erythematous areas. The neck was thick and short; the chest was round, with a protuberant sternum, and the scapulas were large and winged. The abdomen was prominent, with a pendulous, reducible umbilical hernia. The liver and spleen were enlarged. The patient walked with a limp due to shortening of the right leg. The extremities were small as compared with the head and trunk. The distal ends of the long bones were decidedly thickened. The hands were thick and large, with thickened fingers that could not be extended fully. There was dorsal kyphosis in the lumbar region of the spine. Examination of the heart and lungs gave normal results. On a single observation, the blood pressure in the arms was 132 systolic and 100 diastolic. In the legs it was 180 systolic and 110 diastolic.

The left eye showed internal strabisumus with extreme cloudiness of both corneas. Under the slit lamp, the deeper layers of the cornea were seen to contain numerous, small, highly refractile bodies. The ocular tension was normal. The intelligence quotient was 22.

Laboratory Examination: The routine blood count was normal except for leukopenia (4,600 cells); no eosinophilic granulations were seen in the white blood cells. Reactions to the Kolmer tests and the tuberculin test were negative. Urinalysis, smears of splenic and sternal bone marrow and blood lipid determinations for fatty acids, total cholesterol, phospholipids and total lipids revealed nothing abnormal. The oral galactose tolerance test showed a retention of 4 mg. of galactose at one hour.

Roentgenologic examination of the skeleton showed the usual changes of gargoylism. The ends of the long bones were widened and flared, with obliquity of the articular surfaces of the radius and ulna of each arm. The metacarpal, carpal and metatarsal bones were irregularly widened. The contour of the vault of the skull at the apex was irregular, and the sella turcica was greatly enlarged. The vertebral bodies were irregular, with anterior notching particularly prominent

in the first lumbar vertebra. The roentgenologic changes in cases 3 and 4 of this paper were illustrated elsewhere.[4]

Gross Description.—The autopsy was performed twenty hours after death by Dr. Harding Clegg. The body measured 88.4 cm. in length. The head was unusually large. The parietal measurement was 11.7 cm. The frontal-occipital measurement was 18.2 cm., and the circumference was 53.3 cm. The frontal portion of the vault was extremely prominent in the region of the anterior fontanel. The papillae of the tongue were hypertrophied, and the tongue was slightly enlarged. The teeth were small and loosened. A hydrocele on the right side was present. The costochondral junctions were enlarged, and medial to them the cartilages showed well defined, longitudinal grooving. The heart weighed 120 Gm. It was entirely normal throughout except for the mitral valve, which showed a row of firm, fibrous, nodules 1 to 2 cm. in diameter, along the line of closure, with shortening and thickening of the chordae tendineae. The left lung weighed 140 Gm. The upper lobe was well aerated. The lower lobe was mildly congested. The right lung weighed 250 Gm. The upper and middle lobes were within normal limits. The lower lobe was consolidated because of large numbers of coalescing tubercles, 1 to 3 mm. in diameter. Some of the hilar lymph nodes were enlarged and many tubercles were present in their parenchyma. The liver was unusually large and extended 4 cm. below the right costal margin. Except for pallor, the parenchyma showed nothing unusual. The gallbladder was normal. The thymus gland had a normal appearance and measured 2.5 by 7.5 by 1.5 cm. The spleen weighed 150 Gm. The splenic parenchyma had a pale pink color and was firm, smooth and glistening. The pancreas weighed 30 Gm. and showed nothing unusual. Each kidney weighed 60 Gm. The surfaces were smooth, and corticomedullary differentiation was excellent. The adrenal glands, gastroenteric tract and testes were entirely normal. The sella turica was large and shallow. Lying in it was the pituitary gland, which measured 1 by 1.5 by 0.5 cm. No differentiation into anterior and posterior lobes could be demonstrated grossly. The posterior clinoid processes were large and measured 0.8 cm. in thickness.

The brain weighed 1,200 Gm. It appeared normal both externally and on section.

Microscopic Description.—Scattered lymphocytes and large mononuclear cells were present about the blood vessels in the pericardium. Numerous myocardial fibers were vacuolated in their central portions. With scarlet red, these vacuolated cells contained pale, gray, granular material with no demonstrable lipid substance. A large coronary artery in the interstitial tissue showed a pronounced fibrous thickening of the intima with narrowing of the lumen. The adjacent interstitial connective tissue was increased in amount, loosely arranged and heavily infiltrated with deposits of pale, grayish granular material. This same type of connective tissue lay within the endocardium, where some of the connective tissue cells had swollen cytoplasm filled with the amorphous, agranular, grayish substance which did not stain as lipid material. Most of the mitral valve consisted of dense, hyalinized connective tissue, with only small amounts of more fibrillary material. The majority of the connective tissue cells were oval, and the cytoplasm was filled largely with grayish granular substance. While staining with scarlet red showed numerous small, pale orange lipid vacuoles in these cells, this lipid material did

4. (*a*) Cordes, F. C., and Hogan, M. J.: Dysostosis Multiplex (Hurler's Disease; Lipochondrodysplasia; Gargoylism): Report of the Ocular Findings in Five Cases, with a Review of the Literature, Arch. Ophth. **27**:637 (April) 1942. (*b*) Reilly and Lindsay.[1]

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not account for all the increase in the amount of cytoplasm. Lipid substances were also demonstrated in these cells as fine, pale violet globules with the nile blue sulfate stain, and as fine, bluish black granules with Fischler's stain. These altered cells had small oval nuclei with a fine chromatin network. Some nuclei contained bar-shaped chromatin masses.

Sections of the lung showed numerous coalescing caseous tubercles. The intervening alveoli were atelectatic and often contained lymphocytes, plasma cells and large mononuclear cells. The mononuclear cells showed distention of their cytoplasm with gray, granular amorphous material.

The majority of hepatic portal spaces were extremely small and poorly defined. The central veins were often thickened and hyalinized. Irregular strands of pale hyaline connective tissue ran throughout the parenchyma and occasionally connected portal spaces, but often the strands extended through the poorly defined lobules. The parenchymal cells were all altered. The nuclei were round and had a normal appearance. The cells were distinctly outlined with a dense, eosinophilic cellular membrane. The cytoplasm was almost entirely clear but contained small

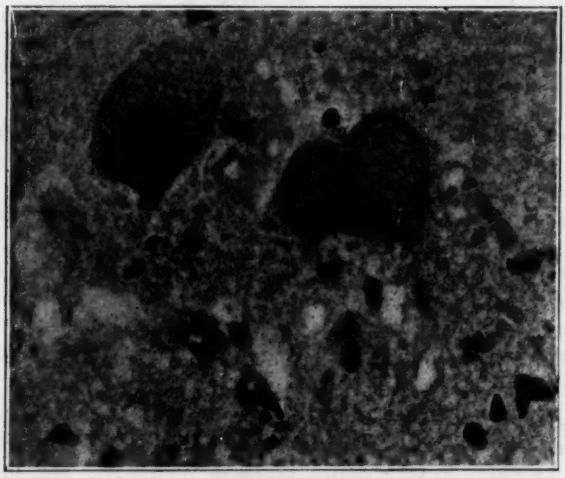

Fig. 2.—Photomicrograph showing nerve cells of medullary nuclei (case 3). Several cells contain localized masses of granular material in one portion of the cytoplasm, while the remainder of cytoplasm is normal; hematoxylin and eosin; × 500.

amounts of granular, eosinophilic material. Only a few cells contained orange lipid globules with the scarlet red stain.

In general, the splenic malpighian bodies were fewer and smaller than normal. In the pulp large numbers of reticuloendothelial cells lined the sinusoids. The majority of these cells were distended with granular nonstaining material. Macrophages with a similar appearance were present in the sinusoids.

The majority of renal glomeruli were normal, though several showed epithelial crescents. In the intercellular portion of these structures, gray, pale granular material was deposited. Most of the convoluted tubules were normal. Almost all the collecting tubules showed epithelial swelling with deposition in the cytoplasm of fine, granular, nonstaining material. This change differed from common cloudy swelling in that the cellular outlines were distinct even adjacent to the lumens.

The cytoplasm of the connective tissue cells between the collecting tubules showed the same cytoplasmic swelling, as well as the presence of the granular nonstaining material described previously.

Practically all the tubular and interstitial cells of the testes showed similar cellular alteration, including the swelling and clearing of the cytoplasm which contained granular, gray nonstaining substance. Many of the tubular epithelial cells and nuclei were two to three times the size of the majority of tubular cells. No lipid substance was demonstrable with the scarlet red stain.

The three layers in the adrenal cortex showed little tendency to differentiation. The epithelial cells were distinctly outlined and contained abundant fat as shown with scarlet red. The cells in the medulla were swollen and vacuolated, and their cytoplasm contained material similar to that seen in other cells. The lobules of the thymus gland were of moderate size but contained relatively few lymphocytes. The majority of reticular cells in the medullary layer were swollen and contained the usual gray granular substance.

In the cerebral cortex, almost all the nerve cells showed striking alteration. They were swollen, rounded or oval, and the cell processes were usually lost. Some nuclei were displaced to the periphery of the cell, and nucleoli were often absent. Some cells and some nuclei were shrunken. The cytoplasm consisted of grayish granular nonstaining material, which replaced almost all the Nissl substance. With scarlet red the cytoplasm stained pale orange. The cytoplasm had a purplish black, granular appearance with Cajal's gold chloride-mercury and ash bichloride stain. Only small amounts of the cytoplasm stained with silver carbonate. Fewer cells contained no nuclei and consisted simply of large, rounded masses of granular gray cytoplasm. The glial cells, which were present in normal numbers, showed no apparent alteration. The subcortical fiber tracts were not altered. The nerve cells of the medullary nuclei showed similar changes. A few cells contained localized masses of granular material in one portion of the cytoplasm, while the rest of the cytoplasm had a normal appearance and normal amount of Nissl substance

In the anterior lobe of the pituitary gland, the majority of cells were of the chromophobe variety. The eosinophils were few in number, and their granules were indistinct. Well formed, distinct basophils were not present. A few cells with basophilic cytoplasm were noted, but this was hyalinized and homogeneous and showed no granulation. All the chromophobes were altered. The nuclei tended to be small, shrunken and pyknotic. The cytoplasm was clear and vacuolated and resembled parenchymal cells seen elsewhere in that it contained fine gray, nonstaining granular material. The posterior lobe was not identified in the sections.

No distinct epiphysial line was visible at a costochondral junction. Instead of the usual columns of ossifying cartilage and bone, a thin transverse plate of bone lay adjacent to the cartilage. The cortical layer of the rib was thin, and the bony spicules of the marrow cavity were narrow and irregular. The periosteum was thickened and moderately cellular. The cartilage cells, most of the osteocytes of the shaft of the rib and the connective tissue cells of the periosteum showed the same changes described in other organs, including swelling of the cytoplasm, with the presence of pale gray, nonstaining granular material. The nuclei were shrunken and pyknotic.

The squamous epithelium on the surface of the cornea was thicker than normal. Just beneath the epithelium and replacing Bowman's membrane was a row of corneal connective tissue cells which were swollen and had a clear or faintly granular grayish cytoplasm. No lipid material was present with scarlet red. The connective tissue cells between the corneal fibers showed similar but less distinct alteration. The corneal lamellas were widely separated by the distention of the

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cytoplasm of the cells. Descemet's membrane was not altered, but the endothelial cells on the posterior surface of the cornea were swollen and had clear, vacuolated cytoplasm.

CASE 4.—*Clinical History.*—D. P., a 3½ year old boy, born Feb. 13, 1937, was admitted to the University of California Clinic on Oct. 3, 1940.

The family history disclosed that the patient had a normal twin sister. One placenta was described at birth. The patient had an older brother (case 3), who also had gargoylism. Another sister died at 5 months of age, supposedly of thyroid disease.

An umbilical hernia was noted at birth. Nothing else unusual was observed until the patient was 5 months of age. When he began to sit up, lumbar kyphosis was noted. By the time the child was 1 year old, the parents had noted the large head, the large hands with partially flexed fingers and the general similarity to the older brother with gargoylism. This patient, in contradistinction to his brother, was still increasing in height and weight. The twin sister, however, was of normal height and had a large vocabulary. The patient could hear, but he did not talk and indicated his wants with gestures. His mental growth was severely retarded.

On his entry to the clinic, the patient's height was 87.5 cm., and his weight was 14.5 Kg. He presented the classic picture of gargoylism. The head was large, and frontal bosses were prominent. The eyes were widely spaced. The mandible was broad, and the mouth was large with widely separated teeth. The tongue was large and thicker than normal, but it was not enlarged to the degree seen in the patient's brother. The typical saddle nose with flaring nares was also present. The neck appeared extremely short. The abdomen was protuberant, and a large, reducible umbilical hernia was noted. The extremities were relatively small, with thickened, large hands and feet. A large, plateau-shaped kyphosis was in the lumbar region. The hearing was not impaired. The edge of the liver was enlarged to 7 cm., and the spleen to 3.5 cm. below the costal margins. Both organs were smooth and firm. The typical clawed hands with limited extension of joints were observed. Clinically, nothing unusual was noticed on examination of the heart, but an electrocardiogram showed auricular extrasystoles. The blood pressure in the arms was 124 systolic and 60 diastolic, and in the legs 132 systolic and 70 diastolic.

The eyes were mildly exophthalmic, and the lids were heavy. The ocular tension was normal. Both corneas were slightly widened, enlarged and uniformly hazy. The pupils showed no abnormality, and the examination of the fundi gave negative results. Examination with the slit lamp revealed typical grayish punctate dots scattered throughout the corneal stroma, which were most conspicuous in the deeper layers.

Laboratory Examination: Routine blood counts were normal except for moderate leukopenia, with the white blood cells numbering approximately 4,200 per cubic millimeter; a moderate scattering of eosinophilic granulations was noted in the white blood cells. The same alteration was observed in cells obtained from the bone marrow. Smears from the bone marrow otherwise showed nothing abnormal. No intracellular lipid material was discovered in the marrow. An oral galactose tolerance test gave normal results. Blood lipid studies showed the following: total fatty acids, 420 mg.; total cholesterol, 298 mg.; phospholipids, 238 mg., and total lipids, 807 mg., per hundred cubic centimeters. The Kolmer and tuberculin tests gave negative reactions. The urine was normal.

Roentgenologic Examination: The findings were practically identical with those of the brother. The bone age was 3 years, while the chronologic age was 3½ years.

The patient died of bronchopneumonia at the Sonoma State Home eighteen months after entering the clinic. His age at death was 5 years.

Gross Description.—The autopsy was performed ten hours after death by Dr. Josephine Williams. The head was enlarged and measured 14 by 20 cm. in diameter and 57 cm. in circumference. Several loops of small intestine were in the umbilical hernia. The costal cartilages appeared partially calcified. The heart weighed 120 Gm. The mitral valve measured 5 cm. in circumference, and it showed nodular thickening along the free edge. The other valves were normal. The aortic valve measured 3.75 cm., the tricuspid valve 7 cm. and the pulmonary valve 4 cm. The right lung weighed 230 Gm. and the left lung 200 Gm. The apex and posterior portions of the right lung were grayish blue and partially consolidated. In the lower lobe the consolidation was patchy. The upper lobe was crepitant.

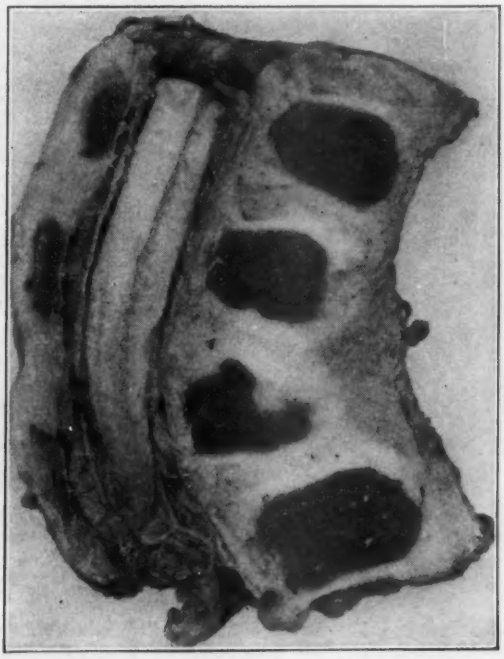

Fig. 3.—Portion of lumbar part of the spine (midline section showing abnormalities which produce dorsal kyphosis (case 4); × 1.2.

The upper lobe of the left lung was well aerated, but the lower lobe was firm, dark red and consolidated. The liver weighed 1,000 Gm. The cut surface showed an unusual pallor, but otherwise it was grossly normal. The spleen weighed 200 Gm. The capsule was slate blue, smooth and shining. The cut surface showed nothing remarkable. Each kidney weighed 60 Gm. The capsules stripped easily, and the cortical surfaces were smooth and shining. The cut surfaces were pale, but the corticomedullary differentiation and the other markings were distinct. The thymus gland weighed 18 Gm. and had a normal gross appearance. The gallbladder and pancreas were normal. The skull was denser than normal. The dura was adherent to the anterior portion of the left frontal lobe. The brain weighed 1,380 Gm. Mild symmetric dilation of the lateral ventricles was observed. Small cystic cavities

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were scattered throughout the white matter of the cerebral hemisphere. The cerebral convolutions were moderately flattened. The sella turcica was shallow, and the clinoid processes were not present. The pituitary gland was of normal size and consistency. The adrenal glands were small, each measuring approximately 2 mm. in thickness. The cornea measured 1.5 mm. in thickness. Its surface was smooth, and the structure was cloudy, although vascularization was not evident. Each of the lumbar vertebral bodies had an abnormal appearance. On cross section the bodies were surrounded with wide zones of glistening hyaline connective tissue which varied considerably in thickness. The bony portions of the bodies were oval or rectangular with rounded corners. The first lumbar vertebral body tended to be wedge shaped, and an irregular mass of cortical cartilage extended into the substance of the vertebral body (fig. 3). This had produced the dorsal kyphosis.

Fig. 4.—Photomicrograph showing changes in the glial cells of cortical layers (case 4); hematoxylin and eosin; × 500.

Microscopic Description.—The pleura was thickened and moderately infiltrated with lymphocytes and macrophages containing pigment. Fibrous thickening of the alveolar walls with infiltration of lymphocytes and plasma cells was noted. The alveolar epithelium was unusually prominent. These cells were cuboidal, and many had sloughed into the alevolar lumens. The bronchiolar walls showed fibrous thickening, infiltration with chronic inflammatory cells and desquamation of the epithelium. The bronchial cartilage was distinctly altered. The cells were usually large and completely filled the lacunar spaces. The cytoplasm was composed of a loosely arranged basophilic network with clear vacuolar spaces between. Some of the alveolar epithelial cells showed distention of their cytoplasm with fine, gray, granular material.

The lymphoid follicles of the spleen were smaller and less numerous than usual at the age. The splenic pulp was not altered.

The kidneys, pancreas and adrenal glands showed nothing unusual. The thymic lobules were large and contained many lymphocytes in the cortical layers. A few Hassall corpuscles were present. In the interlobular septums were scattered mononuclear cells with abundant, pale gray, fine, granular cytoplasm. Some cells had no nuclei. Normal numbers of chromophobes, basophils and eosinophils appeared to be represented in the anterior lobe of the pituitary gland. Many of the cells, especially of the chromophobe group, contained fine, gray, granular material filling their cytoplasm.

In the cornea, Bowman's membrane was replaced with a thin zone of large oval connective tissue cells, the cytoplasm of which was distended with grayish blue, pale, finely granular material. The nuclei were moderately hyperchromatic, small, slightly oval and round. The corneal lamellas were irregularly separated and frayed. This frayed appearance was less distinct in pyroxylin sections but did not appear to be artefact. The cells between the corneal fibers showed the same distention of their cytoplasm by the almost colorless, granular material, accounting for the separation of the lamellas. Involvement of the subendothelial layer of the cornea extended to the limbus.

Definite disorganization of the cerebral cortex with a decrease in the number of nerve cells and loss of the distinct cortical layers was apparent. The majority of cortical nerve cells were swollen, large and rounded and had often lost their processes. The nuclei were displaced, degenerated or absent. The cytoplasm contained material of a fine, grayish blue, granular appearance, which had replaced the Nissl substance to a large extent. The cytoplasm of the glial cells in the cortical layers showed similar change to a lesser degree (fig. 4). The cystic structures in the subcortical tissues described previously consisted in perivascular accumulations of macrophages with abundant, clear, vacuolated cytoplasm.

The cortex of a rib was thin and irregular and varied considerably in thickness. The majority of cells of the periosteal connective tissue, the osteocytes and the cartilage cells showed exactly the same change: they were large and their cytoplasm was grayish, granular and abundant. The osteocytes and the cartilage cells completely filled the lacunar spaces. The central portion of the costal cartilage contained a small collection of loosely arranged connective tissue cells with the same alteration in the cytoplasm. Similar cells lay in groups in the outer portions of the marrow cavity. The cavity contained normal numbers and proportions of hemopoietic elements.

Sections from the first lumbar vertebral body showed extreme irregularity of the epiphysial line, and orderly rows of cartilage were not apparent. All the cartilage cells, both of hyaline cartilage and of fibrocartilage, in the intervertebral disks, as well as the osteocytes, showed the usual distention of cytoplasm by granular, gray material. The cartilage cells had an irregular arrangement, and portions of the chondromucin appeared granular, degenerated and fibrillary. The bony trabeculae of the vertebral body were thin and irregular and showed no osteoblastic activity. Fragmented necrotic trabeculae containing no osteocytes were present. The hyaline cartilage extended well into the vertebral body and was separated from the bone by a layer of dense connective tissue. The cells of this layer showed the same granular, pale cytoplasmic distention as seen elsewhere. The underlying trabeculae were compressed, and the intervening marrow spaces were largely obliterated.

In this case, several different staining methods were used. It was observed that, in general, hematoxylin and eosin stains made on frozen sections showed the grayish blue basophilic material in the cells to stain more deeply and distinctly than that of sections embedded in paraffin. When tissues were placed in a dilute

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solution of formaldehyde U.S.P., which was saturated with calcium salicylate, this grayish blue staining of the cytoplasm was even more distinct with the hematoxylin and eosin. In the nervous system, the scarlet red stain showed pale yellow or colorless granules in the altered nerve cells. These granules stained dark blue with a nile blue sulfate stain, dark brown and indistinct with Fischler's stain and as fine black granules with the Loyez stain.

CASE 5.—*Clinical History.*—J. H., an 18 month old boy, was observed in the University of California Clinic for a six month period. The family history was noncontributory. The mother had several episodes of bleeding early in pregnancy. One year after the patient's delivery, the mother was again pregnant. A fetus 7.5 cm. in length was delivered by therapeutic abortion. Fetal tissues showed no histologic evidence of gargoylism when compared with tissues from a normal fetus of the same age. Two subsequent therapeutic abortions and sterilization were performed; tissues from these fetuses were not examined histologically. At birth, the patient weighed 4,300 Gm., and his head was noted to be large. His mental development was retarded, and he vomited often during the first year of his life. Curvature and kyphosis in the thoracolumbar portion of the spine appeared at the age of 3 to 4 months. He sat up at 6 to 7 months of age and started to walk holding onto a chair at 18 months. He did not talk, and his hearing was poor. His first tooth appeared at 11 months. His corneas were clouded, but his vision did not appear to be impaired. Recurrent rhinitis began at the age of 8 months and was associated with heavy and difficult breathing.

Physical examination showed an infant with typical gargoylism, having a large head (circumference, 51 cm.) covered with coarse hair. He resisted all examinations and did not respond to any command. The skin on most parts of the body, especially the back and legs, was covered with hair. There was no pubic hair, however. The eyes were widely spaced. Both corneas showed the typical haze in the deeper layers. A congenital pupillary membrane, more pronounced on the left side than on the right, was present. The fundi were normal. While the eyes were prominent, true exophthalmos by measurement did not exist. The nose was broad and short with a sunken bridge. There was a profuse mucopurulent nasal discharge. The jaws had 8 peg teeth; the tongue was large and appeared to fill the buccal cavity. The tonsils were hypertrophied and injected, and the uvula was enlarged. Postnasal discharge was profuse. The neck was short. The chest was broad. The lungs were normal. The heart was not enlarged to percussion, and the sounds were clear. No murmurs were heard. The abdomen was enlarged and soft. There was no umbilical hernia. The edge of the liver was not palpable. The spleen was felt 1 to 5 cm. below the costal margin. The back showed a prominent lumbar kyphosis and pronounced hirsutism. The kyphosis was mobile and painless. The fingers and elbows failed to extend fully, and the hands were held in a clawed position. The knees seemed to have complete mobility.

Laboratory Examination: The blood showed moderate leukopenia, with a normal differential count. Seven to 8 per cent of neutrophilic leukocytes showed eosinophilic granulations. The sternal marrow showed a white cell count of 120,000 per cubic centimeter, with a normal differential count; no granules could be found in the leukocytes. Urinalysis revealed nothing abnormal, and the reaction to the Kolmer test was negative. Lipids in the blood measured as follows: total fatty acids, 398 mg.; total cholesterol, 250 mg.; phospholipids, 230 mg., and total lipids 732 mg., per hundred cubic centimeters. Roentgenograms showed widening of the suture lines of the skull. All the bones showed increased trabecular markings. The long bones were shortened, club-shaped and widened in their epiphysial ends.

Metacarpal and metatarsal bones showed irregular development. The spine was deformed, with kyphosis and irregular development of the vertebral bodies, especially in the thoracolumbar region. The epiphysial age was normal. Intelligence testing (California first year and preschool mental scales) revealed an intelligence quotient of 48, and on the Kuhlmann-Stanford scale it was 51 per cent.

The patient died at the Sonoma State Home at 4 years of age of cardiac failure associated with pneumonia, atelectasis and ascites.

Gross Description.—The autopsy was performed twenty-seven hours after death by Dr. Josephine Williams. The head measured 19 by 21 cm. in diameter and 55 cm. in circumference. The heart was enlarged and weighed 220 Gm. After fixation in dilute solution of formaldehyde U.S.P., it weighed 148 Gm. (normal weight at 4 years, 73 Gm.). The pericardial surface was smooth and glistening. A small amount of pericardial fat was present. The left ventricular wall averaged 1 cm. and the right ventricular wall 0.8 cm. in thickness. Just distal to the aortic valve were several small, oval, elevated, pale yellow plaques in the aortic intima.

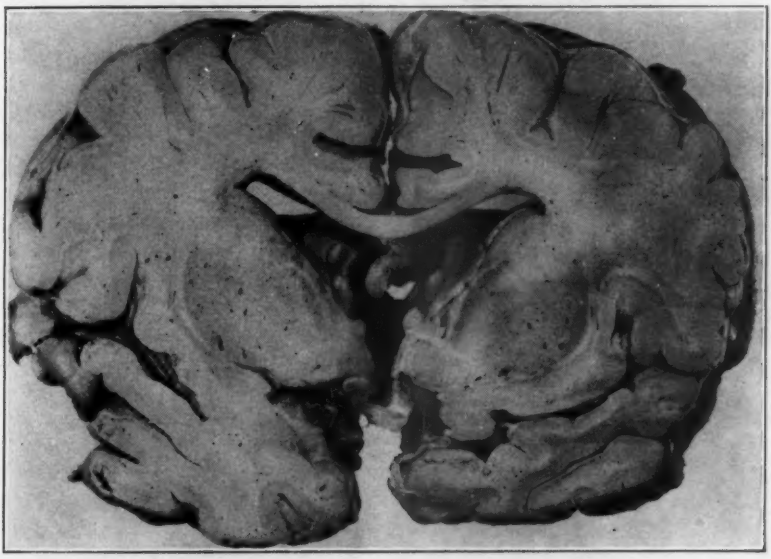

Fig. 5.—Cerebrum (case 5) showing multiple perivascular cysts.

The valves measured as follows: aortic, 4 cm.; mitral, 4 cm.; pulmonary, 4.5 cm., and tricuspid 8 cm. The aortic and pulmonary valves were normal. Slight nodular thickening along the free edge and the line of closure of the mitral and tricuspid valves was seen. The chordae tendineae were shortened. On the left side they did not appear thickened, but they were slightly thickened on the right. The myocardium and endocardium were not altered. All the main coronary vessels showed extreme thickening of their walls due to deposition of grayish, translucent material within the intimal layer. This process left small cleftlike lumens in these vessels. The left lung weighed 180 Gm. and the right lung 320 Gm. The pleural surfaces were smooth and shiny. The parenchyma of both lungs was moderately congested and edematous in the lower and posterior portions. The upper lobes were crepitant. A small amount of clear yellow fluid was present in the left pleural cavity. The liver weighed 1,100 Gm. Its parenchyma was firm and distinctly pale.

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No evidence of cirrhosis was seen. The spleen weighed 200 Gm. The capsule was firm and reddish purple. The parenchyma showed nothing abnormal. The lymphoid germinal follicles were normal and prominent. The gallbladder had a normal

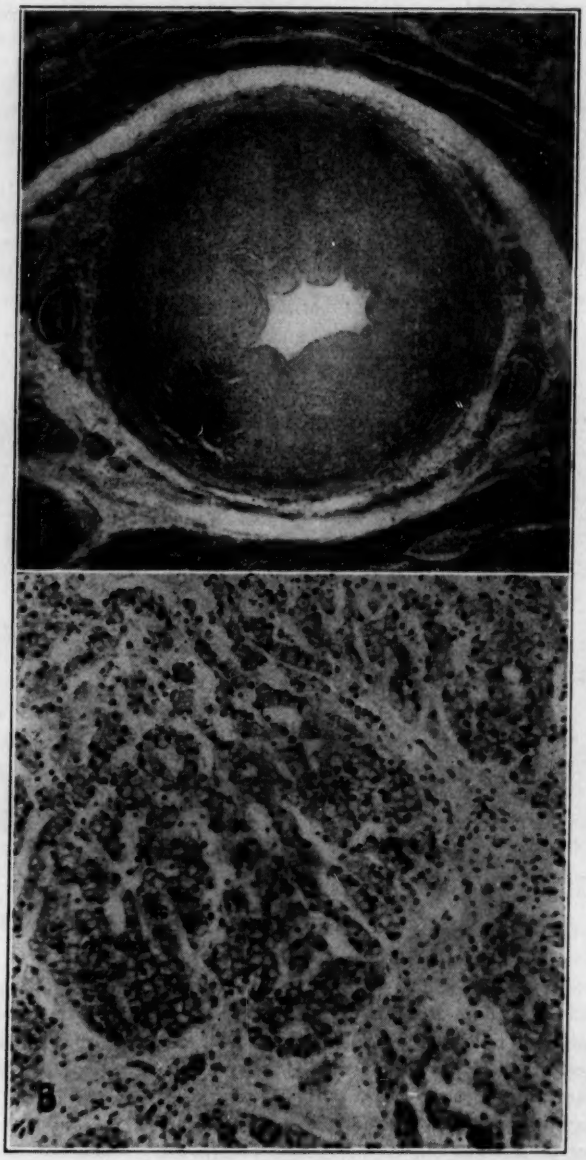

Fig. 6.—Photomicrographs showing, *A*, coronary artery (case 5) with narrow lumen caused by intimal thickening; hematoxylin and eosin; × 23; and, *B*, connective tissue cells in liver (case 5); hematoxylin and eosin; × 45.

appearance. The spleen was normal. One main pancreatic artery showed mild eccentric thickening of the intima. The right kidney weighed 135 Gm. and the left kidney 105 Gm. The capsules stripped easily. The surfaces were smooth and shiny.

The corticomedullary markings were distinct. The anterior fontanel was not closed and measured 2.5 by 2 cm. A longitudinal external bony ridge was present in the midline of the skull. The brain weighed 1,460 Gm. The arachnoid overlying the cerebral hemispheres was opaque but not thickened. The cerebral convolutions were large and well formed, and the sulci were of normal depth. No gross alteration in the arteries at the base of the brain was observed. The lateral ventricles were moderately and symmetrically dilated (fig. 5); the third ventricle and the aqueduct were also moderately dilated. The fourth ventricle was not altered. The ependyma of the lateral ventricles appeared thickened and had minimal brownish pigmentation. The cortical layers of the cerebral hemispheres were widened and had an unusual, gray, translucent appearance. Scattered throughout this layer were numerous small, yellow, opaque zones of softening. In the white matter of the cerebral hemispheres and within the basal nuclei were numerous small cystic spaces measuring less than 1 mm. in diameter. These spaces were filled with translucent, soft mucoid material. These cysts were occasionally seen on longitudinal sections and were found to correspond to the course of the blood vessels (fig. 5). This cystic change was most apparent in the occipital lobes. The pineal gland was absent. No gross alteration in the cerebellum or brain stem was seen.

Microscopic Description.—The outlines of fat cells of the pericardial layer were indistinct. Mild lymphocytic infiltration of this layer had occurred. The myocardial fibers were often mildly vacuolated. Many of the connective tissue cells of the myocardial interstitial tissue beneath the endocardium were enlarged and had abundant, almost entirely clear cytoplasm. The nuclei were oval or round. No alteration in the small coronary veins and arteries was observed. The main coronary arteries and the larger branches had narrow cleftlike lumens, the result of extreme intimal thickening (fig. 6*A*). The media was thin and atrophied. The endothelium was intact. The thickened intimal layer was composed of moderately cellular connective tissue with irregular bands of somewhat hyalinized amorphous collagen of abnormal appearance. Between the fibers were either clear spaces with no visible cells or altered connective tissue cells with oval or rounded nuclei and abundant, clear, well outlined cytoplasm. Both the mitral and the tricuspid valves were composed of connective tissue with a similar appearance. Clefts between the connective tissue fibers were fusiform and were occupied by swollen fibroblastic cells with oval nuclei. The endothelium overlying the valves was intact, and no inflammatory reaction or vascularization was visible. Frozen sections stained with hematoxylin and eosin showed that the altered connective tissue in the endocardium, the intima of the coronary artery and the cardiac valves contained cells with pale, grayish blue amorphous, finely granular cytoplasm. In tissues which had been fixed in a dilute solution of formaldehyde U.S.P. saturated with calcium salicylate, this grayish blue staining of the cytoplasm was slightly more distinct. With scarlet red, these connective tissue cells contained faint-staining, orange, granular cytoplasm. Again the staining density was somewhat more intense in those tissues fixed in dilute solution of formaldehyde U.S.P. saturated with calcium salicylate. No lipid material was evident with the nile blue stain. Only an occasional cell contained a faint bluish black granule with the Fischler stain.[5] No refractile material was seen in the examination of unstained frozen sections with the use of polarized light.

Serous fluid was present in many of the pulmonary alveoli. Some of the epithelial cells lining the alveoli were swollen and prominent, and in many the cyto-

5. Mallory, F. B.: Pathological Technique: A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and Microphotography, Philadelphia, W. B. Saunders Company, 1938.

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plasm was clear and vesicular. None of these cells contained lipid material with the usual lipid stains.

The hepatic cells were approximately normal in size but showed great alteration. The nuclei were normal and usually displaced to one side of the cell. The cytoplasm was abundant and coarsely vesicular. The cells lay in narrow cords separated by widened sinusoids which were almost free of blood. The connective tissue in the portal spaces was increased in amount and had a loose network arrangement. Many of the connective tissue cells had clear, distended cytoplasm. Connective tissue strands tended to unite adjacent portal spaces, thus outlining individual lobules (fig. 6*B*). Hematoxylin and eosin stains made on frozen sections showed faint bluish gray cytoplasm in the hepatic cells. With scarlet red, only a few cells about the central veins contained lipid globules. The majority contained no lipid substance. These lipid masses stained dark bluish violet with the nile blue stain. Fischler's stain[5] revealed no lipid substance. Small, thin, refractile rods,

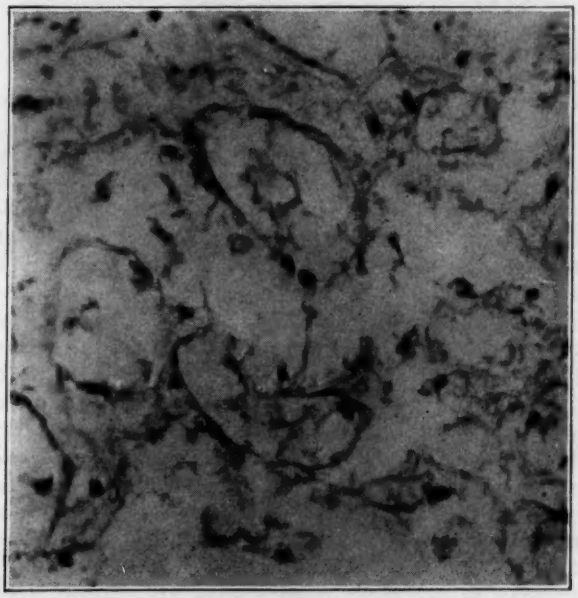

Fig. 7.—Fragmentation of glial fibers of posterior lobe of pituitary gland (case 5); hematoxylin and eosin; × 500.

usually extracellular, were seen with polarized light. In hepatic tissue fixed in dilute solution of formaldehyde U.S.P., embedded in pyroxylin and stained with Best's carmine, only an occasional cell was observed to contain glycogen. Best's carmine, mucicarmine and ruthenium red stains made on frozen sections of tissue fixed in dilute solution of formaldehyde U.S.P. showed no staining of the cytoplasm. The same stains made on frozen sections of tissue fixed in dilute solution of formaldehyde U.S.P. saturated with calcium salicylate showed no stainable material in the cytoplasm of the hepatic cells.

The malpighian follicles of the spleen were large but did not contain germinal centers. The splenic pulp had a loose arrangement. The reticuloendothelial cells were enlarged, and their cytoplasm had many clear vacuoles. Only a few such cells showed black granules with Fischler's stain. No lipid material was present

with scarlet red and nile blue stain. The parenchyma of the pancreas was not significantly altered. A large pancreatic artery showed changes similar to those described for the coronary vessels. The intima was moderately thickened and was composed of hyaline connective tissue which contained large, oval or round fibroblastic nuclei lying in clear, fusiform spaces between the connective tissue fibers. A few of these cells contained bright orange lipid when stained with scarlet red.

The reticuloendothelial cells of the lymph nodes showed the same alteration, with swelling and vesiculation of the cytoplasm, as seen in the splenic pulp.

The adrenal glands and kidneys showed no significant changes. The interstitial tissue of the posterior lobe of the pituitary gland was edematous and the glial fibers were fragmented (fig. 7). Almost all the cells in the anterior lobe were extremely altered. They were enlarged and indistinctly outlined, and they had abundant cytoplasm which was almost entirely clear. In some cells the cytoplasm was bubbly and vesicular. Fewer of the cells had a more homogeneous, eosinophilic, nonvacuolated cytoplasm. No distinct eosinophilic cells were noted. The nuclei were small and rounded and tended to be pyknotic.

The aortic media had an unusual appearance. The elastic connective tissue fibers were unusually distinct and were separated by fusiform clefts containing altered connective tissue cells. These corresponded to fibroblasts and had oval or round, rather small nuclei and a large amount of clear cytoplasm. In a few cells, a small amount of faintly granular eosinophilic material was evident. Widening of the intimal layer was pronounced. It consisted of similar swollen connective tissue cells with clear cytoplasm, separated by a pale-staining, hyaline fibrous tissue. Hematoxylin and eosin stains made on frozen sections showed that these altered connective tissue cells had grayish blue, faint-staining cytoplasm. A few of the connective cells in the inner portion of the intima showed fine, pale, orange lipid granules with scarlet red. These appeared as pale-staining, bluish pink granules with the nile blue stain. Fischler's stain showed no lipid substance. However, when this stain was made on tissues fixed with dilute solution of formaldehyde U.S.P. saturated with calcium salicylate, large portions of the outer intima and media contained bluish black granules in the intercellular substance. No intracellular granules were present. In one portion of the intima were large groups of refractile, spindle-shaped rods seen with a polarized light.

In the subserosal layer of the diaphragm were numerous, large, fibroblastic cells with eccentric nuclei and abundant clear, vesicular cytoplasm.

The subarachnoid space overlying the cerebral cortex was widened and contained an increased number of collagenous fibers. The fibroblasts present had oval or round nuclei. Their cytoplasm was increased in amount and was distinctly vesicular. The cerebral cortex presented a disorganized structure with considerable loss of normal architecture. The majority of nerve cells were greatly altered. The processes were usually absent, and the cells were enlarged and tended to be oval or round. The nuclei were eccentrically placed. No Nissl substance was present in the cytoplasm of these altered cells. The cytoplasm had a finely granular, vesicular character. The majority of blood vessels, especially in the underlying fiber tracts, were surrounded with wide spaces which contained irregularly fragmented, collagenous fibers separated by wide clear spaces. A few fibroblasts were present and showed the enlargement, and vesiculation in the cytoplasm seen in the fibroblasts elsewhere. In the hematoxylin and eosin stains made on frozen sections, the cytoplasm of the nerve cells stained more distinctly and was grayish blue. Numerous amorphous masses, probably representing cells which had lost their nuclei, showed a similar staining reaction. In tissues fixed in dilute solution of formaldehyde saturated with calcium salicylate, hematoxylin and eosin produced a more

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distinct, deeply staining, grayish blue appearance of the cytoplasm. Pale-staining, orange granules were seen in the nerve cells with scarlet red. Throughout the gray matter, bright orange, globular masses appeared when stained with scarlet red, and similar lipid substance was seen in the macrophages about the blood vessels. Fischler's stain made on frozen sections revealed no lipid substance, but when made on frozen sections from tissues fixed in dilute solution of formaldehyde U.S.P. saturated with calcium salicylate, the connective tissue cells and macrophages in the perivascular spaces occasionally contained large, bluish black crystals or globules. Small refractile granules or rods were scattered throughout the gray and white matter when viewed with polarized light. Many of these granules had a typical maltese cross outline. The cytoplasm of the nerve cells had a black, granular appearance with Cajal's gold chloride-mercury bichloride stain. The cerebellum showed the same type of alteration in the subarachnoid spaces as did the cerebrum. The Purkinje cells were swollen; their cell processes were gone, and there was loss of Nissl substance. Cytoplasm was grayish blue, with a granular, finely vesicular character in these cells. The nerve cells in the midbrain, pons and medulla showed similar alteration.

CASE 6.—*Clinical History.*—V. R., an 8 month old boy, was admitted to the University of California Clinic on Feb. 20, 1945. He had had unusually dry skin since birth and was subject to cutaneous rashes aggravated by infections of the upper respiratory tract. Development had been slow, and he could not roll over, sit up or hold his head erect. He had an almost constant infection of the upper respiratory tract. The child had been given thyroid substance, 0.006 Gm. three times a day for some weeks without benefit. It was not known when the kyphosis present first developed.

The family history was entirely normal.

Physical examination revealed a child with generally poor development who lay with his extremities everted. His mental development was retarded; he did not sit up, roll over or hold up his head, though at times he followed objects with his eyes. The skin was dry and scaly. The circumference of the head was 46 cm.; the anterior fontanel measured 3 by 2 cm. Slight edema of the eyelids was present. The eyes were normal; no cloudiness of the corneas was observed. The nose showed an accumulation of dried mucus, and a large amount of mucus was in the pharynx. There were no teeth. The circumference of the chest was 45 cm.; flaring of the lower ribs was noted. The heart was of normal size, shape and position. Sinus arrhythmia and an apical systolic murmur were audible. Coarse rhonchi were heard in both lungs. The edge of the liver, which lay 4 cm. below the right costal margin, was firm, nontender and smooth. The spleen was enlarged, firm and smooth, and its edge extended below the left costal margin in the midclavicular line. The scrotum was enlarged because of bilateral hydroceles. Limitation of flexion of the legs was observed. Both the thighs and the feet were held externally rotated and abducted. The ankles were thick owing to moderate edema. The large toes of each foot overrode the adjacent toes to some degree. The back showed lumbar kyphosis with slight scoliosis to the right.

Laboratory Examination: Routine blood counts were within normal limits. No abnormal granules were seen in the polymorphonuclear leukocytes. Examination of the urine showed nothing abnormal. Reactions to the tuberculin and the Kahn tests were negative. Total blood cholesterol was normal. Roentgenograms showed the skull to be somewhat boxlike, with rather prominent frontal bossing. The anterior fontanel was widely patent. The parietal bones showed two symmetric defects in the posterior portion, about 5 by 11 mm. in size. The metopic suture

was still open. The plane of the orbits was somewhat oblique. The sella turcica appeared normal. The first and second lumbar vertebral bodies were imperfectly ossified in their anterior thirds, and kyphosis and a slight rotary scoliosis of the lumbar portion of the spine were noted. The epiphysial heads of the femurs were immaturely developed. The remainder of the skeleton was normal. The skeletal age corresponded to the chronologic age of 8 months. The mental age was definitely retarded; the intelligence quotient was about 50.

The child died at the age of 1 year at the Sonoma State Home.

Gross Description.—The autopsy was performed twenty-four hours after death by Dr. Josephine Williams. The head measured 14 by 14.5 cm. in diameter and 47 cm. in circumference. The anterior fontanel was open and measured 4 by 4 cm. The epiglottis was rudimentary. The laryngeal mucosa was edematous. The heart weighed 70 Gm. The valves measured as follows: tricuspid, 5 cm.; pulmonary, 3 cm.; mitral, 5 cm., and aortic, 3 cm. The left ventricular wall appeared hypertrophied and measured 1 cm. in thickness. The right ventricular wall measured 2 mm. in thickness. The auricular walls were of normal thickness. Along the free edge of the line of closure of the mitral valve were numerous, fibrous, translucent, coalescing nodules, 1 mm. in diameter, covered with an intact endothelium. The chordae tendineae were unusually short and somewhat thickened. The tricuspid valve had an almost similar appearance. The pulmonary and aortic valves were not altered. The myocardium was normal throughout. The left ventricular endocardium appeared thickened and opaque. No thickening of the main coronary arteries was evident. The right lung weighed 150 Gm. and the left lung 120 Gm. Both were covered with a smooth, shining pleura. On the anterior edges of each lung were a few small, subpleural, emphysematous blebs measuring 1 to 2 mm. in diameter. The bronchi were filled with frothy fluid, and edema and congestion of the parenchyma of both lungs were pronounced. No consolidation was evident. The liver weighed 550 Gm. The peritoneal surface was smooth and glistening. The parenchyma was pale and yellowish white, and the central lobular veins appeared as distinct pinpoint zones of congestion. The anterior margins were rounded and tense. The spleen was enlarged and weighed 60 Gm. Normal, distinct malpighian follicles were visible on the cut surface. The pulp showed nothing unusual. The gastroenteric tract was normal. The kidneys were normal except that the cortical layers appeared pale, yellowish and opaque. The thymus gland weighed 16 Gm. and had a normal appearance for the age. The trachea, larynx, thyroid gland and mediastinal lymph nodes were normal. Some desquamation of the epithelium lining the esophagus had taken place. The costochondral junctions were slightly enlarged, but the epiphysial lines were only slightly wavy and were not thickened. The bodies of the lumbar vertebrae were somewhat oval on sagittal section. There was a posterior bowing with the apex at the second lumbar vertebral body. The latter showed replacement posteriorly with an irregular mass of hyaline cartilage extending into the cancellous bone. The brain weighed 1,070 Gm. and had a normal external appearance. The convolutions of the cerebral hemispheres showed no alteration. The superficial blood vessels were entirely unaltered. The cortical layers of the cerebral hemisphere were less distinctly outlined than normal, and they were apparently separated into an outer and an inner cortical layer. Throughout the white matter, the perivascular spaces appeared as small cystic cavities which measured 0.5 to 1 mm. and contained pale, translucent, mucoid material. Similar changes were present in the white matter of the cerebellum. This alteration was most noticeable in the parietal lobes of the cerebrum and was more obvious centrally than peripherally. The ventricles and the choroid plexus were normal. No alteration in the pons or medulla was evident. The pineal gland was small. The pituitary gland had a normal gross appearance.

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Microscopic Description.—The mesothelial layer of the visceral pericardium was intact. A small amount of loosely arranged fibrous tissue containing scattered lymphocytes comprised the submesothelial pericardial tissue. Many of the myocardial fibers appeared smaller than usual, and often they contained vacuoles in the cytoplasm. The endocardial layer was definitely thickened. It was composed of wide bands of partially hyalinized collagenous material between which lay rows of fibroblastic cells. In cleftlike spaces between the fibers were oval or spindle-shaped nuclei which were surrounded with a small amount of fibrillary or granular material. The outer portions of the cell were indistinctly outlined and were perfectly clear. The mitral valve showed similar alteration in its connective tissue. A few cells contained bar-shaped chromatin masses lying transversely in the nuclei.

The bronchial cartilages were strikingly altered. The lacunar spaces were large and entirely filled with the cartilage cell. The nucleus was surrounded by small amounts of pale, granular fibrillary material with part of the cytoplasm being entirely clear. In many pulmonary alveoli were large numbers of macro-

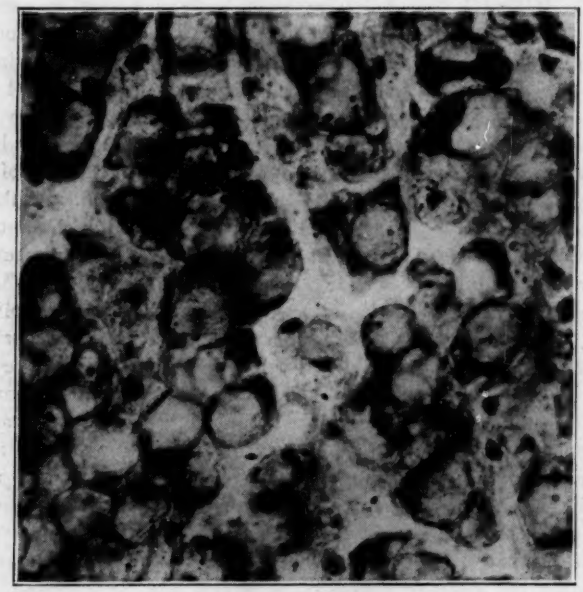

Fig. 8.—Hepatic cells (case 6) stained with scarlet red to show large bright orange-staining lipid globules; × 500.

phages which had a granular, vesicular cytoplasm. Some alveoli were lined with cuboidal cells with a similar-appearing cytoplasm. Other alveoli contained purulent exudate. The tracheal cartilages showed the same alteration as the bronchial cartilages, although in these the matrix was pale and basophilic rather than eosinophilic.

No alteration in the portal or central spaces in the liver was evident, and the bile ducts had a normal appearance. All the hepatic cells were definitely enlarged, and a large, clear vacuole occupied the center of the cell. The nucleus was displaced to one side, but ordinarily it was not significantly flattened. The large central vacuoles were usually clear, but occasionally they contained fine, opaque, granular or fibrillary, eosinophilic material. This area was surrounded with a rather dense zone of eosinophilic cytoplasm. No degeneration, necrosis or cirrhosis

of the liver was noted. A variety of stains were made on the hepatic tissue. With scarlet red stain on tissues fixed in dilute solution of formaldehyde U.S.P., large bright orange-staining lipid globules were seen in many of the hepatic cells, usually lying at the periphery (fig. 8). In some cells the entire central vacuolar spaces were stained as lipid material, although in the vast majority of cells this central vacuolar space remained unstained. No lipid material was visible in the hepatic cells with the nile blue stain. Mucicarmine (for mucin), Best's carmine (for glycogen) and ruthenium red (for pectin) on frozen sections of tissue fixed in dilute solution of formaldehyde U.S.P. gave negative results. Loyez' stain done on tissue fixed in dilute solution of formaldehyde and embedded in paraffin showed no staining of the cytoplasm. Tissues fixed in dilute solution of formaldehyde, embedded in pyroxylin and stained with mucicarmine, Best's carmine, ruthenium red and Loyez' stains showed no staining of the vacuolar material in the hepatic cells. Frozen sections fixed in dilute solution of formaldehyde U.S.P. mordanted with potassium dichromate were stained with scarlet red, nile blue and Smith-Dietrich stains.[5] Sections stained with scarlet red after mordanting with potassium dichromate showed considerably more lipid material than the sections observed without mordanting. The lipid globules tended to lie at the periphery of the cell about the centrally placed large vacuole. The distribution of lipid material was the same with the nile blue stain, and it stained a dark bluish color. No bluish black lipid material was observed with Smith-Dietrich stain. Loyez' stain used on frozen sections of tissues fixed in dilute solution of formaldehyde U.S.P. showed no black-staining lipid material in the cytoplasm of the hepatic cells. All these staining reactions indicated that while lipid material was present in the hepatic cells, it did not account for the distention of the cytoplasm and indicated that some material other than lipid was present in the cytoplasm of the hepatic cells.

The splenic malpighian bodies were small and widely separated, and few possessed germinal centers. Within the sinusoids and intersinusoidal spaces were numerous large mononuclear cells with centrally placed oval or round nuclei, abundant, clear, vesicular cytoplasm and a thin rim of eosinophilic cytoplasm at the periphery. Reticuloendothelial cells lining the sinusoids were not altered.

One of the large renal arteries at the junction of the cortex and the medulla of one kidney showed pronounced alteration. The muscle fibers were extremely vacuolated and had small hyperchromatic, pyknotic nuclei. The internal elastic membrane was distinct, and the other layers of the vessels were normal. No alteration in the glomeruli was evident. The convoluted tubular cells were swollen, and many were degenerated or necrotic.

The gallbladder and pancreas showed nothing abnormal. Almost all the squamous epithelial cells of the esophageal mucosa had abundant, clear cytoplasm, increasing in amount from the outer layer inward toward the lumen. The nuclei were centrally or eccentrically placed with a thin rim of fine, granular, eosinophilic cytoplasm at the periphery. The rest of the cell consisted of a clear, vacuolar space, occasionally containing a small amount of pale, eosinophilic, fibrillary, granular material. Moderate lymphocytic infiltration of the submucosal layers was noted. The stomach was not altered. The submucosal lymphoid tissue in the terminal ileum was present in large amounts. The majority of ganglion cells had abundant, swollen, clear, vesicular cytoplasm without nuclear alteration. Similar change was present in the ganglions of the appendix.

The hilar and mesenteric lymph nodes had an abnormal histologic appearance. The peripheral lymphoid tissue was reduced in amount, and no distinct follicles were present. The sinusoids were widened and contained great numbers

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of lymphocytes and large mononuclear cells. The latter cells had a striking vesicular cytoplasm, with fine, fibrillary partitions between the individual vacuoles. Only a thin rim of condensed cytoplasm was present at the periphery. The nuclei were usually round or oval, but many showed considerable indentation, appearing to be the result of compression by the vacuoles of the adjacent cytoplasm.

The epithelial cells in the anterior lobe of the pituitary gland had a normal arrangement in alveoli and cords. Eosinophils, basophils and chromophobes appeared to be present in normal numbers. The majority of chromophobes, however, had an unusually large amount of vesicular cytoplasm, and large portions of the anterior lobe were composed almost exclusively of these altered cells. Much

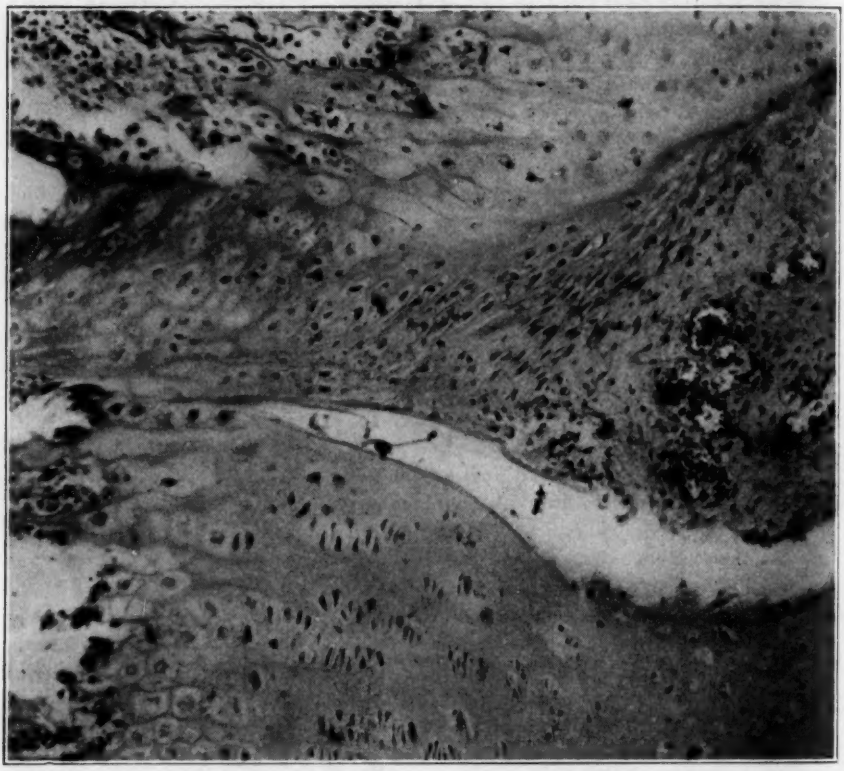

Fig. 9.—Epiphysial line of the rib (case 6). Cancellous bone is interrupted by a mass of vascular connective tissue with many cells of macrophage type; hematoxylin and eosin; × 120.

of the posterior lobe consisted of loosely arranged glial tissue containing various-sized masses of finely granular eosinophilic material. The glial fibers were fragmented and granular, rather than of the usual fibrillary appearance. The cytoplasm of many of the glial cells was unusually abundant and vesicular as well.

Predominant in the parathyroid gland was the chief cell, with fewer numbers of cells of the water-clear variety. The clear cytoplasm of these cells was consistent with the normal cell, rather than with one which was altered, as were many of the other tissue cells in this disease.

The majority of acini in the thyroid gland were larger than normal for the age. The lining cells were cuboidal, and the colloid within the acini was pale and vacuolated at the margins. Many of the epithelial cells had vesicular or vacuolated cytoplasm.

Many of the squamous epithelial cells of the skin contained a large central, clear or granular vacuole in the cytoplasm. This vacuole displaced the nucleus to one side, indenting it and often leaving it crescentic. The dermal layer was of normal thickness and appeared edematous because of separation of the collagenous fibers. Vacuolization of the cytoplasm of the epithelial cells of the hair follicles and the sweat glands was also noted.

A large localized zone of intimal thickening was in the aorta. This tissue was composed of parallel hyalinized connective tissue fibers enclosing spindle-shaped clear, cleftlike spaces. The connective tissue fibers contained flattened, spindle-shaped, fibroblastic nuclei. Some of these cells had an indistinct outline and abundant, clear cytoplasm. The wavy connective tissue fibers in the medial layer were separated in exactly the same manner by spindle-shaped clefts containing fibroblastic cells. The nuclei lying in these spaces were surrounded by small amounts of vesicular or finely granular cytoplasm. The adventitial layer was normal.

The thymic lobules were large and well supplied with small lymphatic cells. Numerous Hassall corpuscles of normal appearance were present in the medullary portions. Throughout the thymic tissue, especially in the medullary layers, were large mononuclear cells with eccentric, round or oval nuclei and abundant vesicular cytoplasm containing eosinophilic fibrils. At a costochondral junction, the osteocytes had small, centrally or eccentrically placed nuclei surrounded with a small amount of pale, fine, fibrillary, granular material appearing to represent residual cytoplasm. The rest of the lacunar space was enlarged and entirely clear. For the most part, the epiphysial line had a fairly normal appearance. The cartilage cells were lined up in rows in a normal fashion, and adjacent to them were thin spicules of newly formed cancellous bone. In the midportion of the epiphysial line (fig. 9), the cancellous bone was interrupted by a large mass of loosely arranged, vascular connective tissue with many large cells of the macrophage type. These cells had centrally or eccentrically placed nuclei with granular, abundant, finely vesicular cytoplasm. This mass of connective tissue replaced the cartilage and the bony spicules adjacent to it in an irregular manner. The cortical layer of the bone of the rib tended to be thin and irregular. It extended well past the epiphysial line and along the margins of the costal cartilage. Large groups of vesicular macrophages lay in the thickened periosteum and extended through openings in the cortical bone into the marrow space. Here they were scattered throughout the hemopoietic tissue. A cross section of the lumbar vertebral bodies described previously showed an unusually wide, irregular cartilaginous layer at the periphery. The lacunar spaces of the cartilage were large and contained distended cells each with a centrally placed nucleus surrounded with granular or fibrillary material. A similar alteration in the fibrocytic cells of the adjacent fibrocartilage (fig. 10*A*) and periosteal connective tissue was present. The nucleus pulposus did not appear altered. Anteriorly, at the point of indentation, the cartilage was deficient and was replaced with dense, fibrous tissue. It appeared as though the vertebral body had collapsed anteriorly because of the unusually thin layer of cortical bone forming the anterior portion of the vertebral body. Within the vertebra the bony spicules were thin. There was little or no osetoblastic activity except at the periphery. The majority of osteocytes were altered as described previously. The same large groups of macrophages were present between

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the irregular spicules of the bone at the periphery of the body along the epiphysial line. They occasionally extended into the cartilagenous masses.

The meninges and blood vessels overlying the cerebral cortex were normal. The cortical layer of the cerebrum was edematous, with separation of the super-

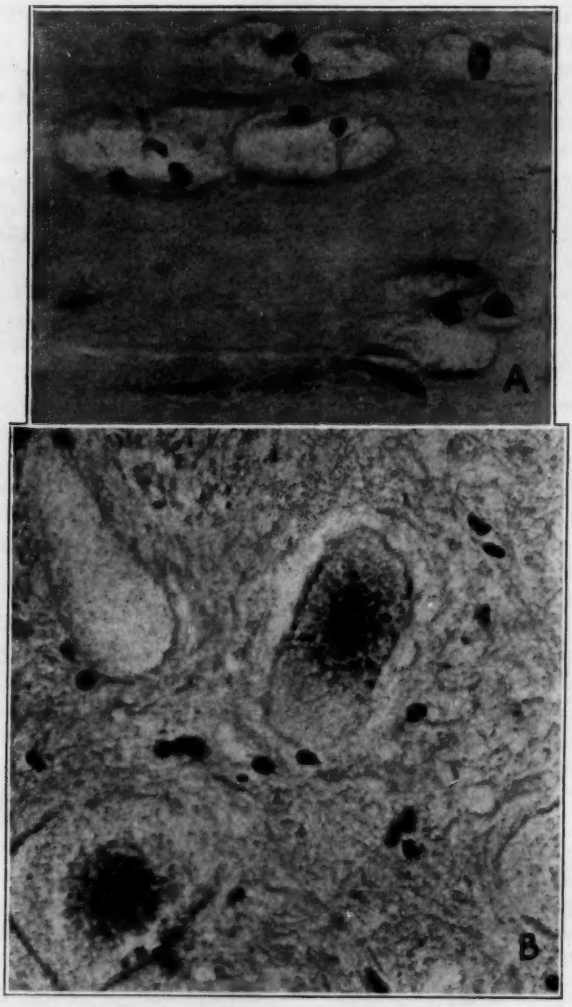

Fig. 10.—*A*, vertebral fibrocartilage (case 6) showing abnormality of lacunar spaces; *B*, cerebral cortical nerve cells with normal nuclei but with distended cytoplasm showing complete loss of Nissl substance. Each section was stained with hematoxylin and eosin; × 500.

ficial and deeper portions. Cortical nerve cells were present in normal numbers, although the layers of nerve cells were extremely irregular. The majority of cells had normal nuclei, but the cytoplasm showed irregular granular and vesicular distention with complete loss of Nissl substance. The cell processes tended to be blunted or absent (fig. 10*B*). The fiber pattern of the cortical white matter was unusually rarefied, with excessive numbers of glial and microglial cells. Little myelin

substance was present in the fiber tracts of the white matter. Nerve cells of the basal nuclei showed changes identical with those seen in the cerebral cortex. Most of the blood vessels in the cerebrum were surrounded with large perivascular spaces containing a small amount of pale, eosinophilic fibrillary material and occasional fibroblastic cells and macrophages both with granular or clear vacuolated cytoplasm. The nerve cells in the spinal cord and medulla showed similar changes. In addition, many cells were of unusually large size and showed distention and disintegration of the nucleus, as well as alteration in the cytoplasm. The cytoplasm had a fine, granular, fibrillary appearance. The changes were present to an equal degree in both the anterior and the posterior horn cells, although few of the latter remained. Many granular ghost cells were present. The Purkinje cells of the cerebellum showed the same changes in the cytoplasm, and, in addition, some nuclei were pale, indistinct and poorly outlined. Perivascular cystic formation and changes in nerve cells were also noted in the deeper layers of the cerebellum.

Case 7.—*Clinical History.*—W. D., a 7 year old white boy, was first seen in the University of California Clinic on Oct. 15, 1946. The family history was noncontributory. The mother and father were 30 years of age at the time of the child's birth. The patient was apparently normal at birth except for unilateral atelectasis. He walked at 11 months and began to talk at 10 months of age. Except for frequent infections of the respiratory tract and occasional episodes of diarrhea, the child appeared well until 20 months of age, when it was noted that he had failed to grow normally and that changes in the extremities suggestive of rickets were present. When he was 2 years of age, lumbar kyphosis appeared. His abdomen became enlarged, his tongue thickened and a cretin type facial appearance developed. He appeared obese. It was noted that the nasal bridge had become depressed; the skin was coarsened, and corneal opacities had appeared. After 2 years of age, his physical and mental development was extremely slow, and eruption of the decidual teeth was retarded. At the age of 6 years, there was loss of speech, apparent cessation of mental development, incontinence and impaired memory. When he was 5½ years old, the joints showed progressive stiffness. Deafness was progressive after the second year.

On examination at 6 years of age, he presented the typical appearance of gargoylism. He was almost totally deaf, and he had a moronic mentality. His voice was hoarse. Pronounced hirsutism of the back was present. The teeth were pointed and typically separated. The palate was high and arched. The mandibular angles were obtuse. The heart was normal to physical examination. No abnormal sounds or murmurs were heard. The lungs were normal. The liver and the spleen extended approximately 8 cm. below the costal margins, and both organs were hard, smooth and nontender.

Laboratory Examination: The red blood cell count and the hemoglobin concentration were normal. The white blood cell count was 3,750 per cubic millimeter, with 55 per cent lymphocytes. The urine was normal. The total blood cholesterol measured 189 mg. per hundred cubic centimeters. The intelligence quotient was 29 per cent.

Examination approximately two months before his death at 7 years of age showed further progression of the disease. Two months before examination he had had measles, which was followed by persistent, chronic, low grade fever and general deterioration. He sat quietly in bed with constant motion of his enlarged tongue. He was almost completely deaf, and his vision appeared to be poor. His hands were short and broad, and the fingers were curved; the nails were unusually soft. Dorsal kyphosis at the level of the first and second lumbar vertebrae

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were prominent. Pronounced hirsutism of the back was present. A wide, keel-like ridge of bone was apparent in the midline of the skull. The ears were relatively large, and their cartilages had a soft, rubbery consistency. The heart was normal on examination except for slight enlargement. The sounds were distant, and the tones were poor. Rhythm was regular. Showers of fine crepitant rales were heard in the lower lobe of the right lung posteriorly. The percussion note over both lungs was hyperresonant. The abdomen was distended, and both the liver and the spleen were decidedly enlarged. An umbilical hernia and bilateral inguinal hernias were present. The musculature of the extremities was wasted, and the skin was dry, scaly and thickened. Repeated examinations of blood films showed large numbers of the typical eosinophilic granules in the neutrophilic leukocytes. His course was progressively downhill, and he died at the Sonoma State Home on Oct. 17, 1946.

Gross Description.—The autopsy was performed forty hours after death by Dr. Stuart Lindsay. The subject measured 106 cm. in length and weighed approxi-

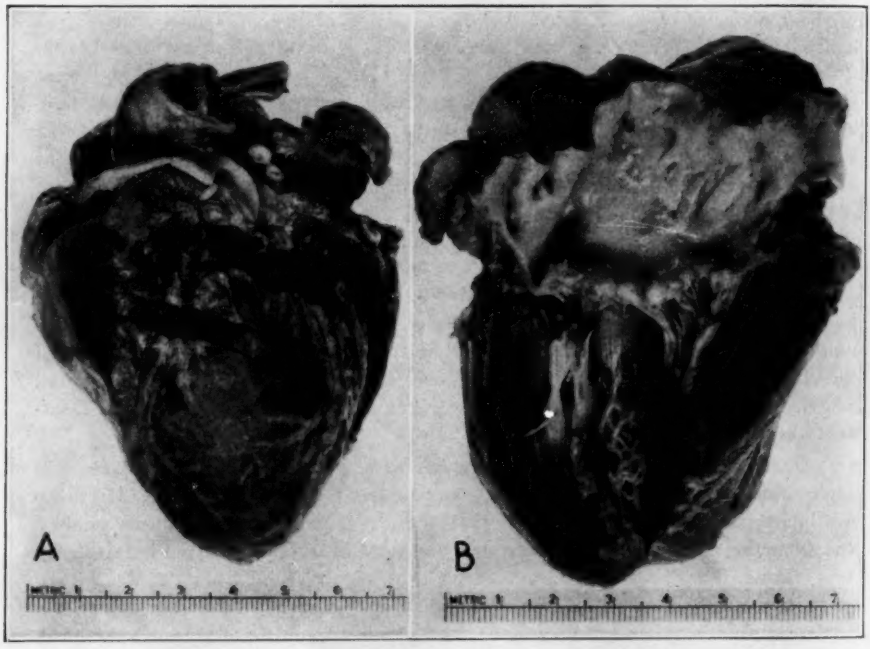

Fig. 11.—*A*, heart (case 7) showing coronary arterial system as rigid white cords on cardiac surface; *B*, heart opened to show altered mitral valve.

mately 18 Kg. The head was relatively large and had the following measurements: circumference, 55.9 cm.; biparietal diameter, 14.5 cm.; occipitofrontal diameter, 19 cm., and frontobregmatic diameter, 19 cm. The vault of the skull was asymmetric, and a prominent midline ridge extended from the lower frontal region almost to the occiput. Biparietal bossing was prominent. The hair of the scalp was sparse. The nasal bone was depressed, and the external nares tended to point anteriorly. Both corneas were mildly opaque; the eyes otherwise were normal. The abdomen was distended, and an umbilical hernia measuring 3 by 2 by 2 cm. was present. Bilateral indirect inguinal hernias were also observed. Bilateral hydroceles were present, and each contained approximately 5 cc. of clear yellow fluid.

Slight dorsal kyphosis with prominence of the spinous process of the first lumbar vertebra was noted. The extremities showed the usual changes of gargoylism, including shortening and broadening of the fingers, which curved toward the radial sides of the hands. The fingers were flexed slightly. The knees and hips showed moderate flexion, with a genu valgum deformity. The feet were slightly everted. All joints showed extreme limitation of motion. On the surfaces of the body were increased amounts of dark hair. The mouth was relatively large, and the mandible was large and angular with bony prominences at the angles and at the level of the first molar teeth on each side. The teeth were widely spaced in both the upper and the lower jaws. The incisors had shallow notches at their biting margins. The upper incisors were carious, and the molars were worn and flat. The tongue appeared enlarged, but it showed nothing remarkable on section.

The liver was enlarged and extended 8 cm. below the costal margin and 10 cm. below the xiphoid process. All the costochondral junctions showed slight widening, and the costal cartilages were bent slightly in a posterior direction. The thyroid and thymus glands were normal; the latter weighed 15 Gm.

The heart was enlarged and weighed 110 Gm. Many irregular zones of opaque thickening of the epicardium of the right and left ventricles were seen. The

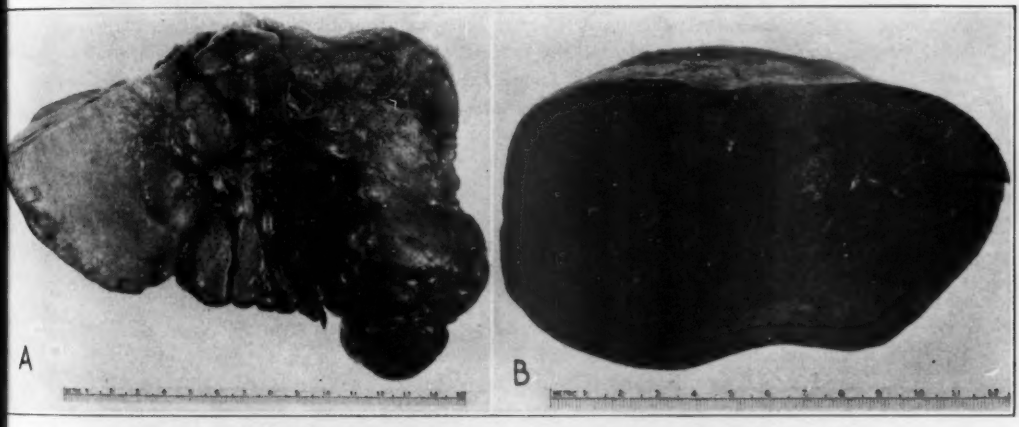

Fig. 12.—*A*, liver (case 7) with abnormal lobulation; *B*, spleen (case 7).

coronary arterial system appeared prominently on the cardiac surface as rigid white cords (fig. 11A). Every vessel showed extreme thickening with only pinpoint lumens remaining. The thickening seemed entirely intimal, with the thickened layer appearing as grayish, moist, translucent tissue. This contrasted sharply with the more compact, opaque medial layer. The left ventricular wall averaged 1.3 cm. in thickness and the right ventricular wall 0.3 cm. The valves measured as follows: aortic, 4.5 cm.; tricuspid, 7 cm.; pulmonary, 4.5 cm., and mitral, 6.5 cm. All the valves showed distinct alteration, which was most striking in the mitral valve (fig. 11 *B*). This cardiac valve showed nodular thickening of the free edge and line of closure. The nodules were coalesced, measuring 1 to 3 mm. in diameter, with a pale grayish yellow, translucent appearance, and were covered with an intact layer of endothelium. Nodules were also present along the edge of the tricuspid valve, being most numerous on the left cusp. The chordae tendineae of both of these valves were shortened, thickened, fibrous and opaque. After fixation in solution of formaldehyde U.S.P., the nodules on the valves showed considerable

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shrinkage. Both the aortic and the pulmonary valves had rolled, thickened edges, which in the midportion of each valve projected toward the ventricular cavities. Much of the endocardium was thickened and opaque, particularly near the aortic valve. The myocardium showed no gross alteration. In the aorta just distal to the aortic cusps were several small, yellowish, elevated, atheromatous plaques. Between these plaques were slightly elevated, striated lesions with a grayish opaque appearance. The pulmonary vessels and bronchi showed no alteration.

The right lung weighed 350 Gm. and the left lung 250 Gm. Most of the anterior and inferior portions of the right lung were adherent to the diaphragmatic and pericardial pleura by a thick layer of partially organized fibrinopurulent exudate. There were considerable congestion and edema of both lungs, most pronounced in the lower lobe and the posterior part of the upper lobe of the left lung. The lower lobe of the right lung was firm and moderately fibrous.

The liver was enlarged and weighed 865 Gm. The anterior edge, especially that of the right lobe, showed a remarkable lobulation with deep indentations between nodular masses of hepatic tissue (fig. 12 *A*). The same gross lobulation was present on the anterosuperior and right lateral surfaces of the right lobe. The anterior edge of the left lobe showed less scarring and indentation. Both the capsular and the cut surfaces of the liver presented a fine, mottled appearance. The lobular markings were unusually distinct, and often individual lobules were seen to be surrounded with narrow bands of translucent fibrous tissue. The parenchyma was extremely pale, and the cut surface had a glistening, yellowish pink appearance. The degree of shrinkage of the hepatic tissue after fixation in solution of formaldehyde U.S.P., was unusually great. Dr. I. L. Chaikoff, of the Department of Physiology of the University of California Medical School, found the total fatty acids of the liver to be 11.4 per cent of the dry weight.

The gallbladder and the extrahepatic bile ducts had a grossly normal appearance.

The spleen was enlarged and weighed 300 Gm. The capsule was smooth and tense. The parenchyma was dark and reddish purple, and the malpighian bodies were not grossly visible (fig. 12*B*).

Each kidney was of normal size and weighed 65 Gm. A mild loss of distinct corticomedullary differentiation had occurred. The cortical layer was thin and measured 2 to 3 mm. in thickness. It was extremely pale and yellowish pink. The medullas were reddish brown but paler than normal.

The rest of the genitourinary tract had an entirely normal appearance.

The gastroenteric tract was normal except for the stomach which was distended with approximately 1,000 cc. of turbid, bile-stained fluid and showed mucosal thickening with a mosaic pattern at the pyloric end.

The pancreas and adrenal glands were normal. Many enlarged lymph nodes were present in the mesentery of the small and large intestine. These nodes measured 0.5 to 1.5 cm. in diameter and had a pale, yellowish pink parenchyma. Bone marrow from several sites was grossly normal.

The thoracic aorta showed numerous, small, longitudinal, atheromatous streaks. These were opaque and yellow and were most numerous about the intercostal openings. In addition, a few, longitudinal, gray, streaklike lesions were seen.

The lumbar vertebral bodies presented an irregular outline on sagittal section. They tended to be oval in shape, and the anterior cartilaginous portion of the first lumbar vertebral body extended into the body of the vertebra. A sagittal section through the right knee joint showed some thickening and irregularity in the epiphysial lines in both the femur and the tibia (fig. 13*A*). The articular surface of the tibia slanted anteriorly, downward and outward at approximately a 45

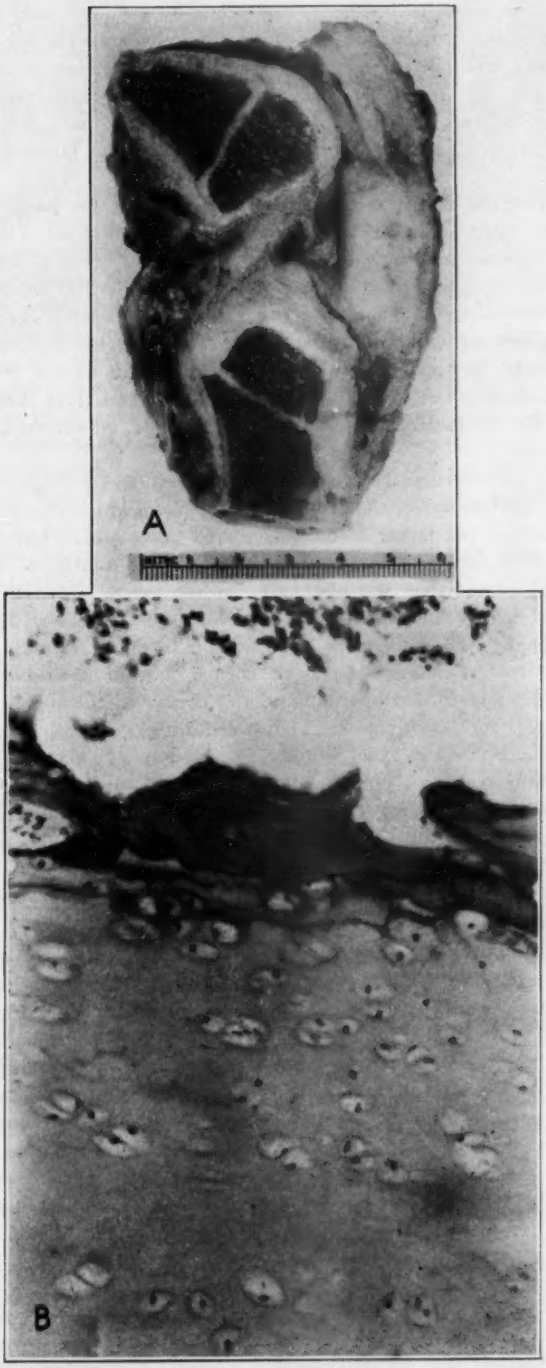

Fig. 13.—*A*, knee joint on sagittal section (case 7) showing thickening and irregularity at epiphysial line; *B*, photomicrograph showing inactive epiphysial line of costal cartilage (case 7); hematoxylin and eosin; × 200.

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degree angle. The articular surface of the femur was smooth and not abnormal. The outer half of the articular surface of the tibia appeared normal, but the inner half of the tibial articular cartilage was thickened and measured 5 to 7 mm. in thickness. It was soft, spongy, yellow and gelatinous in appearance. While the patella was not altered, the suprapatellar ligament near its patellar attachment contained several small zones of translucent material lying between the ligamentous fibers.

The vault of the skull was of normal thickness, but the bone was extremely dense, and the inner and outer tables were not differentiated. On reflection of the dura, the superior and anterior surfaces of the right cerebral hemisphere were covered with an encapsulated collection of approximately 200 cc. of dark brown, viscous, sanguineous fluid. The space containing this material was lined with a thick layer of soft granulation tissue showing considerable staining with blood pigment. A similar but less extensive process was present on the left side, with a collection of approximately 25 cc. of viscous sanguineous fluid. Elsewhere in the cranial cavity the subdural space was lined with a thick, gelatinous layer of yellowish green fibrin.

The brain was of normal size and weight. There was a slight thickening and opacity of the arachnoid over the cerebral hemispheres, which was most pronounced along the course of the larger blood vessels. No gross subarachnoid exudate was seen. The lateral ventricles showed moderate symmetric dilatation, and some dilatation of the third ventricle was observed, but the fourth ventricle and aqueduct were of normal size. The ependyma of the lateral ventricles was edematous, congested and opaque and covered in part with a fibrinous exudate. The cortical layers of the cerebral hemispheres were normal, but in the white matter were many tiny, cystic spaces corresponding to the course of the blood vessels. These spaces averaged 1 mm. in diameter. They were distinctly smaller and less numerous than those described in cases 4 and 6 in this paper. The basal nuclei, pineal gland, cerebellum, midbrain, pons, medulla and spinal cord all had a normal gross appearance. The sella turcica was enlarged, and the posterior clinoid processes were fused together to form a single oval process, measuring 1 cm. in diameter, which extended in an upward and slightly anterior direction. The pituitary gland was of normal size and weight. No other bony deformity of the base of the skull was evident.

Microscopic Description.—The connective tissue of the pericardial and endocardial layers of the heart, as well as the interstitial tissue of the myocardium, were distinctly altered. The fibroblastic cells had swollen, clear cytoplasm, and the nuclei tended to be more rounded than normal. The collagenous fibers were widened, pale, and faintly hyalinized and had lost their usual fibrillary characteristics. The alteration was particularly apparent in the abundant adventitia of the myocardial coronary arteries. Small lymphocystic collections were occasionally seen. Groups of myocardial fibers were replaced with this abnormal fibrous tissue. A few of the larger coronary arterial branches showed intimal and adventitial thickening. The intimal layer was composed of enlarged fibroblastic cells with swollen, clear cytoplasm. All these changes were present to an equal degree in the right and the left ventricular walls but were particularly striking in the endocardial layer of the auricles. The myocardial fibers of the ventricle were within normal limits. Those of the auricular walls, particularly on the left, contained many vacuoles in the myocardial fibers. Alteration in the connective tissue of the aortic and the mitral valves and the adjacent endocardium was present. The fibroblastic cells were greatly enlarged and had an abundant, faintly granular or clear cytoplasm. The nuclei were often displaced to the periphery of the cell. The con-

nective tissue fibers were swollen, had a faint hyaline appearance and were much less fibrillary than normal. The cellular storage reaction appeared more extensive in the superior portions of the mitral valve, although the under surface was involved as well. In the aortic valve the connective tissue cells were even more swollen. Their outlines were indistinct, and they had a large amount of clear cytoplasm. In the central portion of the valve many of the nuclei were absent, and the connective tissue fibers were fragmented and degenerating. Several large calcific deposits were in these areas.

The thyroid acini were larger than normal and were filled with pale-staining colloid. The epithelial cells were cuboidal, and the majority had abundant clear, vacuolated or faintly granular cytoplasm. The capsular connective tissues were composed of swollen, pale, eosinophilic, collagenous fibers, and the fibroblastic cells had increased amounts of clear cytoplasm.

Similar changes were seen in the connective tissue in the thymus gland. The thymic lobules were small and contained fewer than normal lymphocytes. Only a few small, completely calcified Hassall corpuscles were present. In each lobule were diffusely scattered reticular cells which had an increased amount of clear, vacuolated cytoplasm. The attached mediastinal pleura was heavily and diffusely infiltrated with fibroinopurulent exudate.

The squamous epithelial layer of the tongue was of normal thickness, but the outer layer of epithelial cells was abnormal. These cells had a large amount of clear vacuolated cytoplasm. The cellular outlines were indistinct, and intercellular bridges were not visible. The connective tissue beneath the epithelium and throughout the interstitial tissue of the muscle showed fibroblastic swelling and enlargement and swelling, pallor and indistinct striations in the collagenous fibers. The striated muscle, nerves and blood vessels were not altered.

The subepithelial connective tissue of the trachea and the connective tissue about the cartilaginous rings of the trachea showed similar changes. The tracheal cartilage cells were enlarged and had an entirely clear or extremely vacuolated cytoplasm. The remaining nonvacuolated cytoplasm was pale and gray.

Much of the interlobular connective tissue of the lungs showed alteration similar to that described elsewhere. Many macrophages with vacuolated cytoplasm were in the alveolar spaces. Many alveolar groups of both lungs were filled with fibrinopurulent exudate with areas of early organization. In the right lung, considerable intra-alveolar hemorrhage was present. The right pleura was infiltrated with hyaline fibrin.

The splenic capsule and trabeculae resembled the altered connective tissues showing the distinctive changes already described. The lobules were partially outlined by extension of this material from one portal space to an adjacent one. Strands of fibrous tissue also ran through the lobules, dissecting them in various directions. The hepatic cells were larger than normal. Their nuclei, however, had a normal appearance and were of uniform size. The cytoplasm of the hepatic cells was extremely vacuolated, with most of the vacuoles lying toward the central portion of the cell. The cellular membranes were distinct and were lined with a peripheral rim of condensed eosinophilic cytoplasm. The bile ducts and hepatic blood vessels were normal.

The splenic capsule and trabeculae resembled the altered connective tissues already described. The periarterial lymphoid follicles were small and widely separated. The majority of reticuloendotherial cells throughout the splenic pulp had large amounts of pale vesicular cytoplasm.

Much of the interstitial tissue of the pancreas was pale, mucoid and bubbly. A few connective tissue cells were swollen and vacuolated. The ducts, acini and

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islets were normal. Several of the larger pancreatic arteries showed areas of intimal thickening, consisting of large, vacuolated fibroblastic cells. Most of the periadrenal fat cells were of the fetal variety. The connective tissues of the adrenal capsule showed the same changes described previously. The adrenal cortical cells were normal, but the nerve cells of the medullary layer were enlarged and had vacuolated cytoplasm.

The renal glomeruli showed increased epithelial cellularity and few patent capillaries. The basement membranes were widened, frayed and indistinct. Small amounts of precipitated protein were present in the glomerular spaces. Many of the convoluted tubular cells showed cloudy swelling, and their cellular outlines were indistinct. Many cells had lost their nuclei, and the tubular lumens contained granular debris. Moderate vacuolization of the cytoplasm of the cells of both limbs of Henle's loop was noted. The most striking vacuolization of the tubular cytoplasm was in the larger collecting tubules near the renal pelvis. The supportive connective tissue adjacent to the collecting tubules was edematous, and the cells were swollen and vacuolated. Similar alterations were seen in the pelvic connective tissues, though the pelvic epithelium was not altered. The kidney had no vascular lesions.

The submucosal and interstitial fibrous tissues of the muscular layer of the bladder showed the same alteration in the fibroblastic cells and fibers as already described. The cytoplasm of the tubular epithelial cells in the tests showed pronounced vacuolization. The interstitial cells were enlarged, and their nuclei were round, oval and compact. These cells had extensive, clear or vacuolated, poorly outlined cytoplasm. The same alteration in connective tissue was seen in the testicular capsule.

The cells of the prostatic acini were often extremely vacuolated. While the muscular stroma of the gland was not abnormal, the interstitial connective tissue and the connective tissue of the capsule showed the changes already described.

The pericapsular connective tissues of the lymph nodes showed the same changes as seen elsewhere, though the capsules of all the nodes were normal. The peripheral lymphoid follicles were small and indistinct. All the sinusoids were widened, and they were filled with a diffuse syncytial network of indistinctly outlined reticuloendothelial cells. These had small, oval or round, hyperchromatic, compact nuclei surrounded with large amounts of clear, vacuolated cytoplasm.

All the connective tissues of the wall of the gallbladder showed changes similar to those described, and in this organ the fibroblastic cells showed an extreme degree of swelling of the cytoplasm with vacuolization. The connective tissue fibers also were swollen, pale, hyalinized and less fibrillar than normal.

Similar changes were seen in all the connective tissues of the gastroenteric tract, especially that of the submucosa of the stomach and large and small intestine. The mucosal and muscular layers of these segments of the gastroenteric tract were not altered. The nerve cells of the plexuses in the submucosal layers showed striking swelling and vacuolization.

In the sections of the skin from many areas, fibers and cells of the dermal connective tissue showed the usual alteration. The bases of some hair follicles appeared distorted by the adjacent masses of swollen connective tissue cells. The epithelial cells of the sweat glands were greatly enlarged and had clear, vacuolated cytoplasm.

Sections through the wall of the umbilical hernia showed similar changes in the connective tissue, and these were most pronounced adjacent to the peritoneum. This membrane was infiltrated with a layer of hyaline fibrin.

The adventitial connective tissue of the aorta was altered. The fibroblastic cells of the media were rounded and swollen, compressing and distorting the individual nuclei and separating the elastic fibers of the aortic media. The intima was greatly thickened. It consisted of a wide zone of hyalinized collagenous fibrous tissue containing distorted, swollen, vacuolated fibroblastic cells. Beneath the intact intima were a few groups of macrophages with the appearance of foam cells identical with those seen in atherosclerosis. No lipid stains were made.

The bone marrow of the ribs and spine presented a great degree of cellular hyperplasia. No fat cells were present. Few megakaryocytes were noted. Cells of both the myelopoietic and erythropoietic series were increased in number. The myeloid series showed normal maturation, but erythroblasts and a few megaloblasts formed a part of the erythropoietic series. No unusual granules were noted in the cytoplasm of the neutrophilic leukocytes or myelocytes. The reticuloendothelial cells in the marrow were not unusual, and no collections of macrophages were seen.

Skeletal muscle from several areas showed no alteration in the muscle fibers. The perivascular connective tissue resembled that seen in other tissues.

The fibrocartilage of the semilunar cartilage of the right knee showed the same changes in connective tissue as seen in other tissues. The fibroblastic cells were enlarged, and their cytoplasm was clear and swollen. The collagenous fibers were pale, hyalinized and swollen.

The cells of the costal cartilage were enlarged. Their nuclei were round and usually displaced to the periphery of the cell. The cytoplasm was almost entirely clear, though a few granular fragments of cytoplasm were present at the periphery of the lacunar space. The epiphysial line of the costal cartilage showed no growth activity and was replaced with a flat plate of bone (fig. 13*B*). The shaft of the rib was thin and consisted of irregular spicules. Many of the osteocytes showed the same type of enlargement as the cartilage cells. The fibroblastic cells of the periosteum likewise were swollen and vacuolated. The shaft was often perforated by extensions of this altered fibrous periosteal tissue into the outer narrow cavity.

A section through the bone of the skull showed no separation into inner and outer tables. The spicules were wide and had prominent haversian markings. The osteocytes and their lacunar spaces were enlarged. The cytoplasm of the cells was clear or vacuolated. The spaces between the spicules were occupied by blood vessels and large numbers of enlarged, swollen, fibroblastic cells.

Numerous sections of bone elsewhere in the skeleton showed even more striking enlargement of the osteocytic elements. Other epiphysial lines resembled those of the costochondral junctions.

Identical osteocytic changes were seen in the petrous portion of one temporal bone. While many of the marrow spaces were occupied by altered, swollen connective tissue elements, the perineural connective tissue of the eighth nerve was not abnormal. The neural canal had not been encroached on, and the nerve itself had a normal histologic appearance. The osteocytes in the mandible were also enlarged and the marrow spaces were filled with myxomatous, swollen, fragmented connective tissue fibers containing altered fibroblastic cells. The same alteration was seen in the peridental fibrous tissue. The connective tissue of the root canals of the teeth was similarly altered, but the structure of the tooth itself showed no significant changes.

Some of the cells of the marrow spaces corresponded to macrophages which had finely vesicular and granular cytoplasm. The majority of cartilage cells in the epiphysial plates of the lumbar vertebral bodies showed the changes seen in cartilage elsewhere. The nucleus pulposus, however, appeared normal, and the physaliferous cells were not unusually foamy or vacuolated.

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The right suprapatellar tendon showed distinctive changes. The fibroblastic cells between the tendinous fibers were rounded in outline. Their nuclei were oval or round. The cytoplasm was clear and vacuolated except for a few scattered distinctly basophilic granules (fig. 14*A*). The tendinous fibers were less fibrillary than normal and appeared swollen, pale and hyalinized.

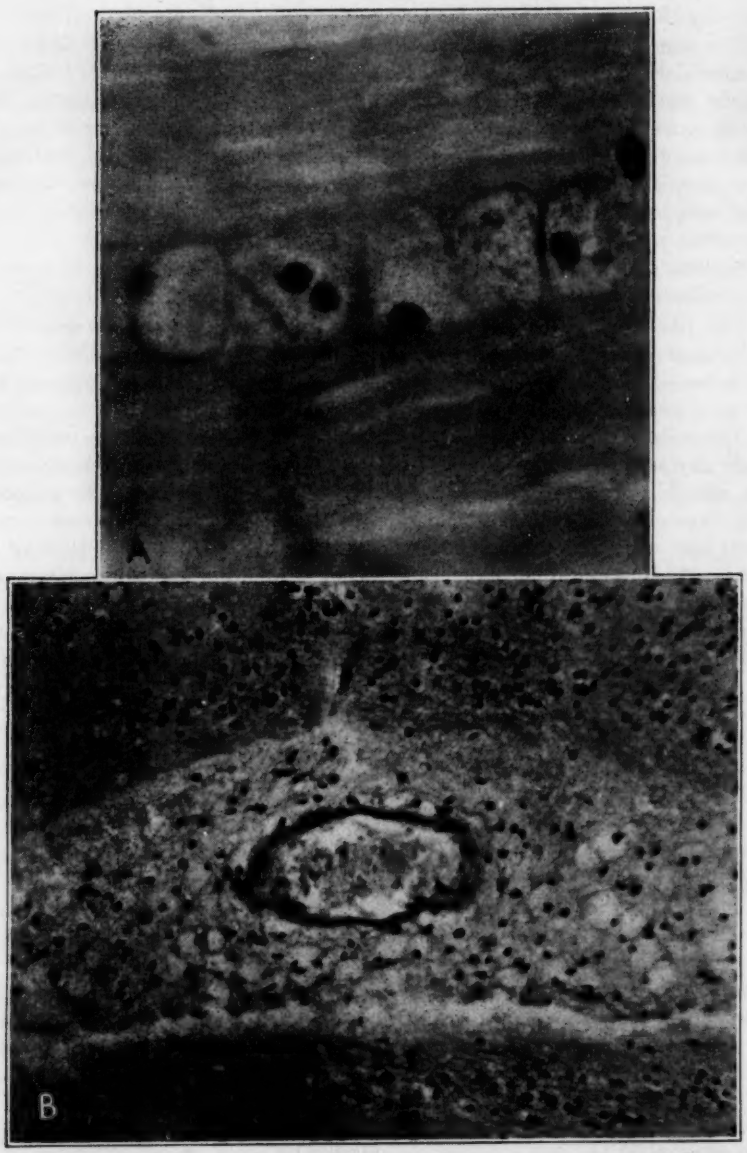

Fig. 14.—*A*, photomicrograph showing changes in suprapatellar tendon (case 7); hematoxylin and eosin; × 500; *B*, cerebrum (case 7) with collection of enlarged adventitial connective tissue cells about a blood vessel; hematoxylin and eosin; × 220.

The epithelial cells of the anterior lobe of the pituitary gland were normally arranged in groups, though almost all the cells were altered. Their cytoplasm was clear or finely or coarsely vacuolated. Some of the cells were larger and had more normal cytoplasm, but none contained distinct eosinophilic or basophilic granules which seemed to be obscured by the cytoplasmic vacuolization. This change was most pronounced in the cells resembling chromophobes. The intermediate lobe was narrow and contained a few small cysts filled with colloid. The glial fibers of the posterior lobe were irregular fragmented, and many of the glial cells had increased amounts of clear, vacuolated cytoplasm.

In the pineal gland, many of the glial and pineal cells also were larger than normal and had increased amounts of clear, vesicular cytoplasm.

The dura was thickened and vascularized. The fibroblastic cells and fibers demonstrated the same swellings and alteration as seen in connective tissue elsewhere. There was a heavy infiltration with neutrophilic leukocytes and macrophages. Many of the latter cells were filled with blood pigment. Attached to the inner surface of the dura in its superior portions were large masses of fibrinopurulent exudate containing large zones of recent hemorrhage. This material was undergoing early fibrous organization.

The subarachnoid space of all portions of the brain contained a moderate amount of purulent exudate. Little protein was present, and the exudate was not organized. This exudate had extended along the perivascular spaces of a few of the superficial cerebral blood vessels.

Sections from all portions of the cerebral cortex showed irregularity of the nerve cell layers. Almost all the cells were altered, especially the larger nerve cells of the deeper layers. These were enlarged and swollen. Most of their cytoplasm had a pale basophilic appearance, with finely divided, scattered eosinophilic granules. The outer portion of the cytoplasm was condensed and eosinophilic. The cells were rounded or oval and had lost their processes. The nuclei were usually displaced to the periphery. Most cells contained no Nissl substance, though a few contained a small amount adjacent to the displaced nucleus. In both the cortical and the subcortical layers, many astrocytes and oligodendrocytes showed an abundance of clear, vacuolated cytoplasm. About the majority of blood vessels in the subcortical white matter were collections of enlarged adventitial connective tissue cells. (fig. 14*B*). These had a large amount of foamy, clear, or faintly eosinophilic, granular, cytoplasm. The majority of these cells were surrounded with a fine reticulum network and were indefinitely outlined. Other cells more closely resembled macrophages. In the basal nuclei were numerous groups of nerve cells showing striking enlargement with loss of processes and Nissl substance. Many cells had lost their nuclei and appeared as rounded or oval, granular, eosinophilic, structureless masses.

The Purkinje cells of the cerebellum showed little alteration, although many of the small nerve cells of the external granular layer of the cerebellum were enlarged and swollen and had abundant eosinophilic granular cytoplasm. Many of these cells had no visible nuclei.

The subependymal tissue of the choroid plexus consisted of enlarged, foamy, clear fibroblasts and macrophages.

The nerve cells of both the anterior and the posterior horns of the spinal cord showed changes comparable to those of the cerebral cortex. In addition, many of the glial cells in the fiber tracts had increased amounts of clear cytoplasm. Mild demyelinization was noted in the anterolateral columns of the spinal cord.

One eye was fixed in Bouin's fluid and embedded in pyroxylin. The cornea of the other eye was excised, and portions were fixed in absolute alcohol and

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Carnoy's solution. The remainder of the second eye was fixed in Bouin's fluid and embedded in paraffin.

The sclera was thickened. The connective tissue fibers were loosely arranged

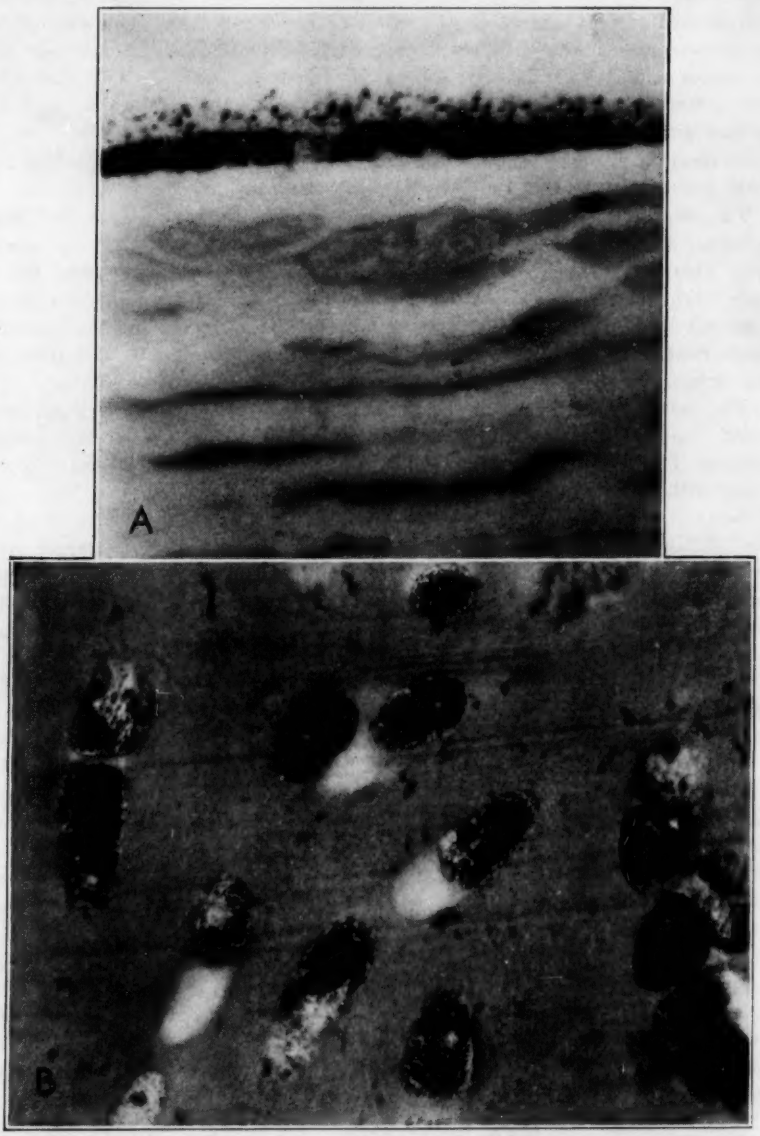

Fig. 15.—*A*, posterior surface of corneal tissue (case 7); cresyl violet; × 820; *B*, costal cartilage (case 9) showing large bright red granules after fixation in absolute alcohol and staining with Best's carmine; × 420.

and appeared edematous and less fibrillary than normal. They enclosed fusiform or spindle-shaped clear spaces containing a displaced, compressed fibroblastic nucleus. In some cells were a few faintly eosinophilic granules.

Many of the nerve cells in the nuclear layers of the retina were enlarged and had clear, vacuolated cytoplasm and displaced nuclei.

The epithelial cells on the surface of the ciliary body and the posterior surface of the iris were greatly enlarged and had eccentrically placed nuclei. The cytoplasm was filled with fine eosinophilic granules in some cells and was vacuolated in others. The connective tissue of the iris, ciliary body and choroid was loosely arranged and edematous and contained numerous macrophages with granular or vesicular cytoplasm.

The corneal epithelium was thin and intact. Some epithelial cells were enlarged several times, owing to clear swelling of the cytoplasm which had caused nuclear displacement. In these areas, Bowman's membrane was fragmented or missing and was replaced with large, fusiform, connective tissue cells having a finely granular cytoplasm. The corneal corpuscles and their processes were swollen, and their nuclei displaced. The cytoplasm was filled with fine and coarse granules. The endothelial cells on the posterior surface of the cornea were uniformly enlarged and cuboidal and had clear, vacuolated cytoplasm. Staining of the corneal tissue fixed in Carnoy's fixative with cresyl violet revealed that these cells were crowded with coarse, uniform, violet granules (fig. 15*A*). This reaction did not occur when the stain was applied to the other tissues fixed in Carnoy's solution. Less heavily staining granules filled the corneal corpuscles. Descemet's membrane was entirely intact. The alteration in the connective tissues of the cornea and sclera was much less evident in the sections in pyroxylin than in those in paraffin.

Sections of all tissues were fixed in Carnoy's solution and in absolute alcohol. Pyroxylin sections were stained for glycogen with Best's carmine stain and the Feulgen-Bauer methods.[6] The only red-staining granular material demonstrated in any of the cells was a few coarse eosinophilic granules in several of the hepatic cells in sections fixed in Carnoy's solution and stained with Best's carmine. Hematoxylin and eosin stains on tissues prepared in the same manner showed coarse, pale basophilic granules in the cytoplasm in the hepatic cells, a feature not present in the tissues fixed in a dilute solution of formaldehyde U.S.P. Tissues fixed in Carnoy's fixation or in absolute alcohol were treated for four hours in a saturated solution of trinitrophenol in dioxane (85 per cent), dilute solution of formaldehyde ("formol") (10 per cent) and glacial acetic acid (5 per cent) and were then stained by the Feulgen-Bauer method for glycogen. This method demonstrated no glycogen, although in case 10 (described later), glycogen was demonstrated by this process in tissues fixed in Carnoy's solution.

The method of staining mucin and glycogen with the use of periodic acid and Schiff's reagent[7] was applied to various tissues fixed in both Bouin's fixative and dilute solution of formaldehyde U.S.P. This method is almost identical with the Feulgen-Bauer method of glycogen staining[6] and depends on the formation of an aldehyde from a carbohydrate by action of an oxidizing agent.[8] In general, the cytoplasmic network stained more distinctly with this method than with those described previously. In many of the squamous epithelial cells of the tongue, and in some of the tracheal cartilage cells, were distinct, coarse eosinophilic granules filling the cytoplasm. In some cortical nerve cells and in the connective tissue cells

6. Bensley, R. R., and Bensley, S. H.: Handbook of Histological and Cytological Technique, Chicago, University of Chicago Press, 1938, p. 105.

7. McManus, J. F. A.: Histologic Demonstration of Mucin After Periodic Acid, Nature, London **158**:202, 1946.

8. Dempsey, E. W., and Wislocki, G. B.: Histochemical Contributions to Physiology, Physiol. Rev. **26**:1, 1946.

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of the mitral valve, finer, less distinct eosinophilic granules completely filled the cell cytoplasm. Only scattered eosinophilic granules were observed by this method in the hepatic cells in tissue fixed in Bouin's fixative, dilute solution of formaldehyde U.S.P., or absolute alcohol. The enlarged perivascular macrophages in the cerebrum had a faintly staining, pink granular cytoplasm by this staining method.

Hepatic tissue fixed in dilute solution of formaldehyde embedded in paraffin showed no staining of the cytoplasm of the parenchymal calls with toluidine blue, thionine, or Löffler's methylene blue.

Case 8.—*Clinical History.*—D. L., a 3 year old Mexican girl, entered the Los Angeles General Hospital on Sept. 23, 1946. The child weighed 3,970 Gm. at birth and since birth had been considered deformed. She had had measles at the age of 1 year and pneumonia on two occasions at the age of 2 years. The family history was noncontributory; she had 2 normal siblings. The child had difficulty in breathing and a chronic coryza, with repeated, frequent acute infections of the upper respiratory tract. Her mental development had been normal. On the evening of her admission to the hospital she suddenly fell forward while walking and was unable to rise. All extremities were flaccid. On entry into the hospital the child's temperature was 40.5 C. (104.9 F.); the pulse was irregular, and its rate was 100. The child was acutely ill and dyspneic and was unable to talk or to move her extremities. The head was enlarged, and the facial appearance was unusual. The anterior fontanel was open and pulsating. The pharynx was extremely injected. The cardiac rate was rapid; no murmurs were heard. There was dulness to percussion over the upper lobe of the left lung. No rales were heard. The edge of the liver was palpable 4 cm. below the right costal margin. The spleen was enlarged, and its lower border was felt about 8 cm. below the left costal margin. The knees were partially flexed. The extremities appeared paralyzed and completely flaccid. The patellar reflexes were absent. Painful stimuli caused no reaction.

Laboratory Examination: Studies of the blood revealed the hemoglobin concentration to be 10 Gm. per hundred cubic centimeters; red blood cells numbered 4,820,000 and white cells, 9,200 per cubic millimeter. The sella turcica was enlarged. Death occurred on Sept. 24, the day following entry to the hospital.

Gross Description.—The autopsy was performed seventeen and a half hours after death by Dr. M. Pearce. The subject weighed 13 Kg. and measured 90 cm. in length. The nose showed a saddle deformity. The skull had an abnormal shape with high, rounded forehead and prominent sloping of the posterior surface toward the occipital region. The neck was unusually short. The fingers were shortened, and both wrists and ankles were thickened. The extremities measured as follows: external malleolus of the ankle to the knee, 20 cm.; knee to greater trochanter, 17 cm.; trunk, 33 cm.; wrist to elbow, 12 cm. and elbow to shoulder, 15 cm. The anterior fontanel was open and measured 2 by 2.5 cm. The thyroid, parathyroid and thymus glands were grossly normal. The pericardium was not altered. The heart weighed 70 Gm. The valves had a normal appearance and measured as follows: mitral, 5.6 cm.; aortic, 3.9 cm.; pulmonary, 3.1 cm., and tricuspid, 6 cm. The coronary vessels were not altered. The myocardium was normal throughout. The left ventricular wall measured 7 mm. in thickness and the right ventricular wall between 1.5 and 2 mm. The aorta and its major branches appeared normal grossly. The pleural cavities were normal. The left lung weighed 100 Gm. and the right lung 130 Gm. Numerous small areas of consolidation associated with generalized congestion and edema were seen throughout both lungs. Abundant mucopurulent fluid was present in the trachea and bronchi. The pulmonary ves-

sels were not altered. The tracheal and bronchial lymph nodes were enlarged and hyperemic. The liver weighed 700 Gm. Its lower margin lay 8 cm. below the costal margin in the right midclavicular line. The external surface was not altered, although both the external and the cut surfaces were pale. The latter surface was rather greasy and soft. The lobular markings were indistinct. The gallbladder, extrahepatic bile ducts and portal vein were normal. The spleen weighed 120 Gm., and its lower margin extended 6 cm. below the costal margin in the left midclavicular line. The cut surface was pale and soft. The entire gastroenteric tract was normal. The intra-abdominal lymph nodes were not unusual. The kidneys weighed 98 Gm. together. The capsules were of normal thickness and stripped easily. Corticomedullary differentiation was excellent, and the renal pelves, ureters and bladder were normal. The internal or external genitalia showed no alteration. The skull, meninges and blood vessels appeared normal. The brain weighed 1,320 Gm., and appeared swollen and edematous. The pituitary gland appeared slightly enlarged. The left adrenal gland weighed 2.1 Gm. and the right adrenal gland 2 Gm. Both glands were within normal limits. The extremities showed flexion contractures of the knees and fingers, which could not be extended fully.

Microscopic Examination.—A few of the tissues in this case were made available to us for study by Dr. Edward M. Butt. The epicardial layer and the myocardial fibers were normal. Some of the perivascular connective tissue and portions of the subendocardial connective tissues were altered. The connective tissue cells had increased amounts of clear, vesicular cytoplasm, and the collagenous fibers were swollen and pale. A similar change was seen in all the connective tissue of the mitral valve, with even more striking swelling of the cytoplasm of the fibroblastic cells. These cells had oval, compressed, hyperchromatic nuclei and unusually distinct cellular membranes. The cytoplasm was filled with fine, faintly basophilic granules. In a few cells, the granules were coarse and uniform. In the deeper portion of the valves, cells were fewer and amounts of condensed collagen were greater. Groups of large macrophages with similar granular cytoplasm lay in clusters beneath portions of the valvular endothelium. An oval, calcific mass was present in the inferior angle formed by the attachment of the valve to the myocardium.

All the hepatic cells were slightly enlarged, and they were outlined by a peripheral zone of condensed eosinophilic cytoplasm. The rest of the cytoplasm was filled with vacuoles separated by narrow eosinophilic strands. The hepatic nuclei had an entirely normal appearance. Coarse fibrous septums ran between some adjacent portal spaces, partially outlining single lobules or portions of lobules.

The lymphoid follicles of the spleen were widely spaced; most of them were small. Cellular pulp containing large numbers of neutrophilic leukocytes and lymphocytes was abundant. The predominant cells, however, were macrophages, many of which had large amounts of granular, vesicular cytoplasm.

The peripheral lymphoid follicles of the lymph nodes were few in number and were small. Throughout the node, all sinusoids were strikingly widened because of the great numbers of macrophages and reticuloendothelial cells. These cells were large and had poorly defined, abundant cytoplasm which was vacuolated and contained small basophilic granules.

The tracheal submucous was heavily infiltrated with lymphocytes. The epithelial cells of the submucous tracheal glands were enlarged; the cellular cytoplasm was more abundant and granular than normal. The cells of tracheal cartilages were also enlarged. Their nuclei were usually displaced peripherally. These cartilage cells occupied the entire lacunar space, and their cytoplasm consisted of vacuoles with remaining granular fragments of cytoplasm between.

Microscopic alterations in the lung, kidney, sympathetic ganglions of the gastroenteric tract, myocardium, bone and cartilage were described by Dr. M. Pearce. His descriptions were consistent with those of lesions in the previously described cases of gargoylism.

All these tissues were stained with Best's carmine stain and the Feulgen-Bauer method after fixation in absolute alcohol and embedment in pyroxylin. None of the swollen, altered cells contained glycogen except a few cartilage cells of the tracheal cartilage. The cytoplasm of these cells was distended with large, uniform, brightly eosinophilic granules, accounting for the cellular enlargement. Lipid stains were not made. Nissl's stain showed eosinophilic granules in the cytoplasm of the Kupffer cells in the liver and in a few of the reticuloendothelial cells of the lymph nodes. Tissue fixed in absolute alcohol and embedded in pyroxylin was treated with the solution of dioxane, formaldehyde, trinitrophenol and acetic acid, as described in case 10, and stained by the Feulgen-Bauer method,[6] no glycogen was demonstrated.

Case 9.—*Clinical History.*—P. P., a 4 year old white boy, a patient of Dr. William C. Deamer, entered the University of California Hospital on May 10, 1946. At birth the child was said to have a congenital pigeon breast, genu valgum and widened epiphyses. Otherwise, development was normal until the age of 3 years, when dwarfism was noted. He had a younger sister with gargoylism. The mother and father were first cousins. When examined at the age of 3½ years, he was about 12 cm. shorter than the average height. The skull was dolichocephalic, and he stood with a crouched stance. Extension of the elbows, hands and knees was limited. Hands were clawed, and bilateral genu valgum was present. The deformity of the sternum was diminishing. The facies were not gruesome, and the nose had only a slight saddle deformity. There was no hirsutism. Cloudiness of the cornea could be detected only with a slit lamp. A basal systolic murmur was heard. The edge of the liver was palpable 3 cm. below the right costal margin and was hard and smooth.

Eosinophilic granulation of the neutrophilic leukocytes was mild. Similar granules were not seen in one study of aspirated bone marrow. Several complete blood counts gave normal results. Reactions to the tuberculin test and the Schick test were negative, while the blood lipid panel and excretion of hippuric acid, as well as the results of urinalysis, intravenous glucose and intravenous galactose tolerance tests, and the insulin tolerance test, were normal. His intelligence quotient was 102 per cent.

A biopsy specimen of the upper epiphysis of the right fibula was taken at the age of 4 years. This tissue was fixed in absolute alcohol, decalcified in 5 per cent nitric acid in absolute alcohol, washed for several days in numerous changes of absolute alcohol and embedded in pyroxylin.

Microscopic Examination.—In sections stained with hematoxylin and eosin, all the cells of the epiphysial cartilage were enlarged and completely filled the lacunar spaces in their chondromucinous matrix. Their nuclei were small, compact and usually displaced to the periphery. The cytoplasm was almost entirely clear but contained a few granular fragments. The fibrocartilaginous cells at the periphery showed identical changes. Large, irregular clefts in the epiphysial cartilage contained blood vessels surrounded with many large macrophages. These had abundant, clear cytoplasm. At the epiphysial line, the cartilage cells were irregularly arranged, and the adjacent osteoblastic columns were thin or absent. Frequently, the epiphysial line was interrupted by large groups of macrophages with clear, vesicular cytoplasm. The cortical layer of the bone consisted of wide, dense

spicules which showed little osteoblastic activity and which were separated by bands of periosteal connective tissue extending into the marrow space. Many of the osteocytes of the cortex were enlarged, completely filled their lacunar spaces and had a clear cytoplasm with a few remaining cytoplasmic granules. The hemopoietic tissue was entirely normal. With Best's carmine stain, most of the cartilage cells and many of the swollen connective tissue and bone cells were filled with large, uniform, bright red granules, presumably glycogen. This stained material was so abundant as to account fully for the cellular swelling and enlargement (fig. 15*B*).

CASE 10.—*Clinical History.*—P. H., a 13 month old white boy, entered the University of California Clinic August 1945 because of dyspnea, restlessness and frequent infections of the upper respiratory tract since birth. Lumbar kyphosis had appeared at the age of 3 months, and an inguinal hernia was first noted at 10 month of age. There was no history of familial diseases or congenital anomalies. The parents displayed no consanguinity, and the patient had no siblings. Pregnancy was full term, and deliverey was normal. The neonatal period was devoid of difficulties for the mother and child. Feeding was normal and adequate. The patient sat up at 4 months and rolled over at 2½ to 3 months, and teeth appeared

Results of Carbohydrate Tolerance Tests in Case 10

Material Tested Dosage Route	Levulose-Glucose-Galactose 1.75 Gm./Kg. (24.8 Gm.)			Insulin 3.4 Units Subcutaneous	Epinephrine 0.4 Cc. of Solution Subcutaneous
	Oral	Oral	Oral		
Fasting	0	134	0	128	130
30 min.	0	176	82	74	176
1 hr.	0	154	27	92	190
2 hr.	0	132	12	76	130
3 hr.	0	128	12	100	108
4 hr.	0	128	0	—	—

at 8 months. At 13 months he was unable to stand unaided, but he could walk with support and was just starting to speak a few words. No other illnesses, accidents or operation had occurred. Systemic history did not disclose other abnormalities in the past. Physical examination at 13 months revealed the typical signs of gargoylism: a large head, enlarged tongue, short neck, cloudy corneas, protuberant abdomen with hepatosplenomegaly and umbilical hernia, clawed hands and disproportionately short legs and arms. He was 76 cm. in length and weighed 11.58 Kg. Other observations of interest were: mongolian spots in the lumbar area, wide separation of the eyes, sheer occiput, patent anterior fontanel measuring 2 by 2.5 cm., closed posterior fontanel, redundant skin over the posterior part of the neck, many rhonchi in the lungs, a loud systolic murmur at the aortic area and along the left sternal border and much fat padding about the suboccipital, cervical and pubic areas.

The infection of the upper respiratory tract subsided after about one week of sulfadiazine therapy. At 13 months the intelligence quotient was 89. Roentgenograms showed a normal bone age, kyphosis at the first lumbar vertebra and the usual changes of gargoylism in the vertebrae, ribs and short and long bones of the extremities and skull. Moderate hypochromic anemia was present; no eosinophilic granulations in the white blood cells were demonstrated. Urinalysis showed nothing abnormal, and Wassermann reactions were negative.

The boy entered the Sonoma State Home at the age of 18 months. He was next seen at 28 months of age when these additional signs had developed: large ears with flabby cartilages, peg-shaped teeth, bushy eyebrows, greatly increased obtuseness of mandibular angles, large umbilical hernia, bilateral inguinal hernias, crouched stance with genu valgum and eosinophilic granulations in the white blood cells. The cardiac murmur was no longer audible, but the heart was enlarged. The subcutaneous tissue was thick and inelastic, but the hair was still soft and silky. Most of the previously noted signs were accentuated. A photograph taken at this time was published previously.[1]

He was next examined by us at 34 months of age, at the University of California Hospital, with the following new developments: He was deaf, spoke little, rarely stood and could not walk. He sat most of the time, was quite irritable and had had a chronic cough. He measured only 83 cm. in length, partly because of flexion of the hips and knees and the kyphosis. He weighed 13.2 Kg. The degree of corneal clouding was increased. The hernias were larger, and the hepatosplenomegaly, the flexion deformities of the extremities and the kyphosis had all increased. The cardiac murmur again was audible. The skin showed a negative reaction to 0.1 mg. of tuberculin. The hemoglobin content ranged between 96 and 82 per cent; the red blood cells numbered 4,800,000 per cubic millimeter. The white blood cell count varied from 10,600 to 23,000 per cubic millimeter. The differential count was normal. A great increase in numbers of eosinophilic granulations in the white blood cells was noted four days after anesthesia induced with ether.

A series of carbohydrate tolerance tests were made (micromethod on capillary blood); values are expressed as milligrams of blood sugar per hundred cubic centimeters in the table.

The intelligence quotient had dropped to 51. The hormonal iodine level of the blood was 6.5 micrograms per hundred cubic centimeters. The blood cholesterol measured 104 mg. per hundred cubic centimeters. Reontgenograms showed an increase in width of the heart and increase of the kyphosis.

With the patient anesthetized lightly with ether, biopsy specimens of the liver and a costal cartilage were taken.

Gross Description.—The specimens consisted of a wedge-shaped bloc of pale brown hepatic tissue 1 cm. in diameter and a thin wedge-shaped block of costal cartilage. Part of each block was fixed in Carnoy's fixative and part in saturated solution of trinitrophenol in dioxane (85 per cent), dilute solution of "formol" (10 per cent) and glacial acetic acid (5 per cent). Sections were cut from the tissue embedded in paraffin blocks and stained with hematoxylin and eosin, Nissl stain and the Feulgen-Bauer stain for glycogen. Part of the tissue was fixed in acetone, embedded in paraffin and stained for acid and alkaline phosphatase.[9]

Microscopic Description.—Liver (Carnoy's fixative):

A. Hematoxylin and eosin: The majority of portal spaces were normal. One contained a large group of lymphocytes. The hepatic capsule was normal, and no cirrhosis was present. The hepatic cells were large and had distinct eosinophilic cellular membranes. Their nuclei were normal and uniform in size. The cellular cytoplasm was almost entirely clear, with a few, scattered, small eosinophilic granules of remaining cytoplasm. Kupffer cells were not easily identified; the cytoplasm of the few seen appeared similar to that of the hepatic cells.

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9. Kabat, E. A., and Furth, J.: A Histochemical Study of the Distribution of Alkaline Phosphatase in Various Normal and Neoplastic Tissues, Am. J. Path. **17**:303, 1941. Wolf, A.; Kabat, E. A., and Newman, W.: Histochemical Studies on Tissue Enzymes: III. A Study of the Distribution of Acid Phosphatases with Special Reference to the Nervous System, ibid. **19**:423, 1943.

B. Feulgen-Bauer method: For the most part, the tissue had the same appearance as that stained with hematoxylin and eosin. Scattered cells beneath the capsule, however, contained a few clumps of bright eosinophilic granules, usually lying at the periphery of the cell.

C. Nissl stain: The cell cytoplasm consisted of a faintly staining, granular network with clear spaces between.

Liver (fixed with solution of dioxane, formaldehyde, acetic acid and trinitrophenol):

A. Hematoxylin and eosin: With this fixative, the tissue stained much more distinctly and deeply. The cytoplasm had the same finely granular characteristics as the sections described previously. A few cells showed more striking vacuolization of the cytoplasm, suggesting lipid infiltration. A few groups of cells lying adjacent to portal spaces were undergoing necrosis and were surrounded with lymphocytes and fewer neutrophilic leukocytes. A few lobules were partially surrounded with narrow zones of condensed fibrous stroma which was infiltrated with lymphocytes.

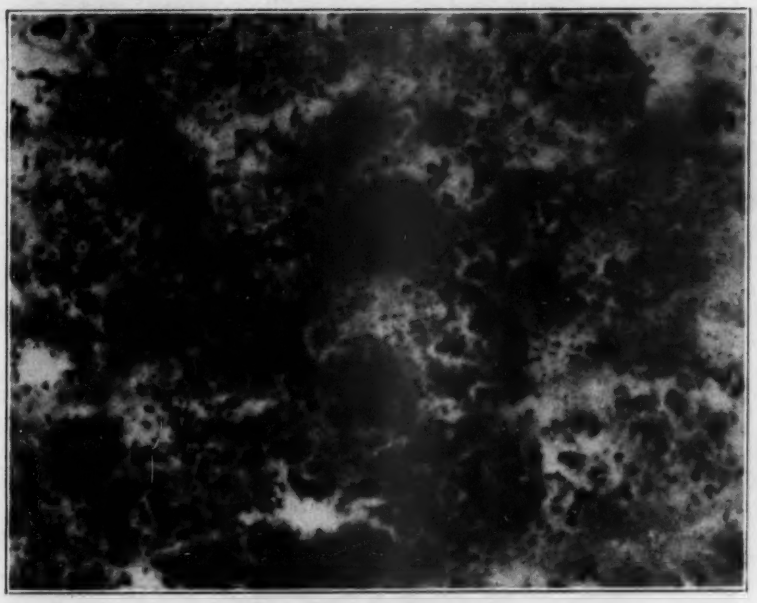

Fig. 16.—Section of liver (case 10) after fixation in solution of dioxane-formaldehyde, trinitrophenol and acetic acid and staining with Feulgen-Bauer method; × 820.

B. Feulgen-Bauer Method: With this stain, every hepatic cell was filled with large coarse, uniform, bright eosinophilic granules (fig. 16). This material fully accounted for the cellular enlargement. The connective tissue cells of the portal spaces contained a few similar granules which appeared to lie in the cell cytoplasm. A few Kupffer cells were identified; these too were distended with large eosinophilic granules.

C. Nissl Stain: With this stain, the cytoplasm was almost entirely clear except for a few, scattered granular fragments of cytoplasm. Kupffer cells were unusually numerous and prominent, in both the sinusoids and the portal connec-

tive tissues. The cytoplasm of these cells contained numerous small, uniform, dark, eosinophilic granules.

Cartilage (Carnoy's fixative):

A. Hematoxylin and eosin: The majority of cartilage cells were not enlarged. Some were elongated and spindle shaped. The nuclei were normal and uniform in size. The lacunar spaces in the cartilaginous matrix were of normal size and were almost entirely occupied by a fine network of faint eosinophilic cytoplasm. The adjacent perichondrial connective tissue cells were swollen and distinctly outlined and had increased amounts of clear, faintly granular cytoplasm. The attached striated muscle showed no alteration. The cartilaginous matrix was normal.

B. Feulgen-Bauer Method: The majority of striated muscle fibers showed bright eosinophilic staining of the longitudinal and cross striations, indicating the presence of glycogen. No eosinophilic granular material was present in the swollen connective tissue cells or in the cartilage cells.

C. Nissl Stain: No granules were evident in the cytoplasm of the connective tissue or cartilage cells.

Cartilage (fixed with solution of dioxane, formaldehyde, acetic acid and trinitrophenol):

A. Hematoxylin and eosin: With this fixative, the cellular detail was more distinct than with Carnoy's fixative. The cytoplasm of the cartilage cells showed less shrinkage, was faintly granular and completely filled out the lacunar spaces. The perichondrial connective tissue and striated muscle were not altered.

B. Feulgen-Bauer Method: The cytoplasm of all the cartilage cells was filled with large, uniform, bright eosinophilic granules. Many of the connective tissue cells of the perichondrium contained fewer but similar eosinophilic granules.

C. Nissl Stain: Many of the cartilage cells were filled with small, uniform, eosinophilic granules, but in the majority of cells these granules did not account for all the cytoplasm. The connective tissue cells of the perichondrium contained many similar granules.

Liver (phosphatase):

A. Alkaline—A few granules in the hepatic cells had a faint brownish color.

B. Acid—In a few lobules most of the hepatic cells contained large, coarse, brown granules.

Cartilage (phosphatases): The hyaline and fibrocartilage cells contained a few faint brown granules in material treated by both methods (acid and alkaline).

Additional staining procedures gave further information regarding the nature of the substance stored in the hepatic cells.

Parallel staining (by the Feulgen-Bauer method for glycogen) was done on the hepatic tissue from this patient and from the liver of a patient with typical glycogenosis (von Gierke's disease). Both these tissues had been fixed in solution of dioxane, trinitrophenol, acetic acid and formaldehyde as was described previously. In both instances, the hepatic cells were filled with large, bright eosinophilic granules; these were smaller and less numerous in the liver of the patient with gargoylism. Further sections, similarly fixed, were then incubated for two hours at 37.5 C. with saliva, followed by staining with the Feulgen-Bauer method. Neither the patient with gargoylism nor the one with glycogenosis showed eosinophilic granules present then in the hepatic cells. Incubation in saliva at room temperature for five minutes showed only mild loss of eosinophilic granular material in the hepatic cells in both instances.

As indicated previously, the Feulgen-Bauer staining method demonstrated eosinophilic granules in only a few of the peripheral cells of the sections of he-

patic tissue fixed in Carnoy's solution. When additional sections were fixed with the solution and treated with the solution of dioxane, formaldehyde, trinitrophenol and acetic acid, which was described previously, for four hours, followed by staining with the Feulgen-Bauer method, abundant eosinophilic granules filled the cytoplasm of the hepatic cells. Substitution of tenth-normal hydrochloric acid (four hours) for the dioxane solution did not give positive staining results with the Feulgen-Bauer stain. Hepatic tissue fixed in Carnoy's solution, treated with dioxane solution as described previously and incubated two hours with saliva at 37.5 C., showed no eosinophilic granules when stained by the Feulgen-Bauer method.

Hepatic tissue fixed in solution of dioxane, formaldehyde, acetic acid and trinitrophenol was stained with toluidine blue solution. Uniform dark, blue granules filled the Kupffer cells. Almost completely filling the cytoplasm of the parenchymal hepatic cells were large, coarse, pale bluish masses. These often were clumped, and some of the larger granules had darker blue centers. Thionine gave a similar cellular staining in the hepatic cells, though the granules in the Kupffer cells had a purplish tint. With Löffler's methylene blue solution, there was no staining of the cytoplasm of the hepatic cells, though dark blue granules filled the Kupffer cells. These three stains were used on hepatic tissues fixed in Carnoy's fluid from the present case and also were made on hepatic tissue fixed in solution of dioxane, formaldehyde, acetic acid and trinitrophenol from a typical case of glycogenosis, with entirely negative results.

CASE 11.—*Clinical History.*—E. N., a girl of Armenian extraction, was a sister of G. N. (case 2), who is reported on in this paper. At the time of writing, this patient was 13 years of age. She showed an extreme picture of gargoylism, with dwarfism, an enlarged, broad head, a short neck, marked abnormal hirsutism, especially over the back, umbilical hernia, clawed hands, extreme cloudiness of the corneas, hepatosplenomegaly, mental retardation and prominent lumbar kyphosis. Photographs and additional clinical records of this patient were published previously.[4] The only tissues available for study were the tonsils and adenoids, which were removed when the patient was 4½ years of age.

Microscopic Description.—The lymphoid, reticuloendothelial or epithelial tissues of the tonsils and adenoids showed no alteration. The subepithelial and interlobular connective tissues had a loose arrangement, and the connective tissue cells showed moderately swollen cytoplasm, resembling the connective tissue seen in the other cases described in this paper.

CASE 12.—*Clinical History.*—R. W., a white boy, was a brother of W. W. (case 1) who was reported on in this paper.[3] He first entered the University of California Clinic at the age of 19 months. His family stated that at birth he resembled his brother with gargoylism, though no unusual symptoms appeared during the first year of life. At 1 year of age it became obvious to the family that the patient had many of the characteristics of gargoylism. On examination, he showed the usual physical signs of a moderately advanced case of gargoylism, though there was no kyphosis. Numerous small white papular lesions were seen on the posterior aspect of the left arm. These were firm and discrete. A specimen of this area of the arm was taken for biopsy with the use of local anesthesia when the patient was 3 years of age. Tonsillectomy and adenoidectomy was performed at the age of 12 years.

Microscopic Discription.—The skin showed subepithelial and perifollicular dermal atrophy, though no characteristic swelling or enlargement of the dermal connective tissue cells was observed. Perivascular lymphocytic infiltration was minimal. Follicular lymphoid hyperplasia of the tonsils and adenoids was pro-

nounced, but no evidence of the storage phenomenon was seen in epithelial connective tissue or lymphoid cells.

REVIEW OF PATHOLOGIC LESIONS RECORDED IN LITERATURE

Although the clinical and roentgenologic manifestations of gargoylism are well known, comparatively few reports of autopsies have appeared in the literature. The first such report was that of an examination by Tuthill[10] of the brain from the patient originally described by Hurler.[11] Nerve cells of all portions of the cerebral cortex, of the basal ganglions, of the nuclei of the brain stem and of the spinal cord were often balloon shaped and puffy and had enlarged dendrites. There was loss of Nissl substance, and the cytoplasm had a netlike quality with fine granules. All cells contained lipid material, which was most abundant in those showing greater degrees of swelling. The neurofibrils of the involved ganglion cells were displaced to the outer borders of the cytoplasm. The cerebral cortical nerve cells were enlarged and also showed a netlike cytoplasm. The adventitia of the vessels of the centrum ovale and basal ganglions was unusually thick. This tissue layer consisted of a delicate fibrous network with numerous large cells which contained clear indefinitely defined cytoplasm. Fine and coarse blue-staining granules were present in the cytoplasm and free in the adventitial spaces, as well as elsewhere in the brain substance. This substance was visible only in material fixed in alcohol stained with aniline nuclear stains. Tuthill concluded that the histologic lesions in this brain were characteristic of juvenile amaurotic idiocy.

In the fatal case reported by Reilly[3] in 1935 (case 1 in this paper), the characteristic changes in the tissues were not generally recognized at that time. Review of the available material in this case in the light of our present knowledge of gargoylism showed most of the typical lesions characteristic of the disease.

Two additional autopsies were recorded by Ashby, Stewart and Watkin[12] in 1937; one was a thorough study of the central nervous system, and the other was an incomplete examination. In both instances the pituitary gland was enlarged, and in 1 the gland was hyperplastic. The thyroid gland in each case was abnormal; in 1, it was fibrotic and atrophic. The authors expressed the opinion that the alteration in the thyroid gland might be responsible for the dwarfism and other manifesta-

10. Tuthill, C. R.: Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas, Arch. Neurol. & Psychiat. **32**:198 (July) 1934.

11. Hurler, G.: Ueber die Typenmultipler Abortungen vorwiegend am Skelettsystem, Ztschr. f. Kinderh. **24**:220, 1919.

12. Ashby, W. R.; Stewart, R. M., and Watkin, J. H.: Chondro-Osteodystrophy of the Hurler Type (Gargoylism): A Pathologic Study, Brain **60**:149, 1937.

tions of the disease. These 2 cases showed no enlargement of the spleen or liver, and histologic study of the liver in 1 showed nothing abnormal. The reticuloendothelial system revealed no histologic evidence of lipid storage. In the cerebral cortex, considerable abnormality of the cytoarchitectonics was evident, and the cortex was diminished in thickness. Everywhere in the central nervous system, the ganglion cells were swollen, pear shaped or spherical. The cytoplasm was filled with an infiltrating substance, displacing the nucleus and the neurofibrils and replacing the Nissl substance. The similarity to the alteration in ganglion cells in infantile amaurotic familial idiocy (Tay-Sachs disease) was noted, although involvement of the cell processes was considerably less. Staining reactions showed a lipid substance in the cytoplasm of the altered ganglion cells; the perivascular interstitial lipid had different staining qualities and was visible with polarized light. Chemical and solubility studies suggested that the lipid substance was a cerebroside, either kerasin or phrenosin, or a mixture of both.

The first indication of the systemic distribution of the disease was seen in the complete autopsy recorded by Kressler and Aegerter.[13] The patient was a boy of Italian descent who died at 8½ years of age of cardiac failure. Clinical observations included clouded corneas, hepatosplenomegaly, mental retardation, dwarfism and skeletal deformities. Postmortem studies revealed many tissues showing evidence of intracellular storage of an unidentified substance, which in the authors' opinion was a complex lipid material. This intracellular substance was gray and opaque in frozen sections stained with thionine. The vacuolated cells gave negative staining reactions with mucicarmine for mucin and Best's carmine stain for glycogen. Lipid stains (scarlet red and nile blue) showed nothing except in those cells normally containing fat.

The myocardial fibers showed swelling and vacuolization. The alveolar and interstitial spaces of the lung contained vacuolated mononuclear cells. Large vacuoles replaced almost all the cytoplasm of the hepatic cells. Lymphocytes and reticular cells of the lymph nodes, spleen and thymus often contained a foreign substance in their cytoplasm. The cytoplasm of the cells of the anterior lobe of the pituitary gland was increased in amount, unstained and clear. Lack of staining was especially notable in the chromophobe cells. Wide separation of the corneal laminas, possibly because of infiltration with the same lipid material, was the only ocular lesion demonstrated. The lesions of the central nervous system were identical with those of the cases of Tuthill,[10] and Ashby and co-workers[12] except for the lack of staining of the infiltrating substance.

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13. Kressler, R. J., and Aegerter, E. E.: Hurler's Syndrome (Gargoylism): A Summary of the Literature and a Report of Case with Autopsy Findings, J. Pediat. **12**:579, 1938.

In a review of gargoylism, Washington[14] summarized the previously reported autopsies and added the histologic changes seen in 4 of his own cases. The widespread granular deposits in brain, reticuloendothelial tissue, heart, endocrine glands and other tissues were observed, but, in addition, it was noted that endosteal cells and osteoblasts of the bone were affected. It was pointed out that an irregular distribution and enlargement of epiphysial cartilage cells indicated failure of growth of cartilage. The adjacent epiphysial bone lay in a horizontal plate instead of in normal vertical rows. Washington expressed the opinion that the skeletal abnormalities, with the exception of those in the vault of the skull, could be explained by this chondrodystrophy. Since he felt that the infiltrating substance was a lipid material, he coined the term lipochondrodystrophy.

In 1944, de Lange and co-workers[15] reported an additional instance of gargoylism. A complete postmortem examination showed no evidence of lipid storage in the involved tissue cells. The patient was a boy who died at the age of 19 years after bronchoscopy. The onset of the disease was at 1 year of age, with difficult walking and standing, followed by protrusion of the abdomen and an umbilical hernia. When 14 years of age, he was dwarfed and showed the skeletal manifestations of gargoylism on both clinical and roentgenographic examination. He was mentally deficient and had a systolic cardiac murmur and hepatosplenomegaly. Examination of the blood and urine showed nothing abnormal. However, an oral galactose tolerance test (40 Gm.) showed elevation of the blood galactose above the normal limits of 40 mg. per hundred cubic centimeters. The autopsy showed cardiac hypertrophy and thickening of the mitral, tricuspid and aortic valvular leaflets. The liver was enlarged, and the surface was irregularly indented, grooved and granulated. The parenchyma was wet and red-brown, with a yellowish tint and fine and coarse protruding granules. Some of the intra-abdominal lymph nodes were enlarged. Splenic enlargement was mild. The pituitary gland was normal in size, though the sella turcica was somewhat widened. Examination of the right elbow joint showed thickening of the articular cartilage and retardation of ossification. Microscopic examination showed some histologic changes not previously reported. The cartilage cells and the perichondrium of the laryngeal and adjacent cartilages had a finely granular cytoplasm staining brownish yellow with scarlet red and, in addition, containing orange-yellow lipid droplets. The chondromucin and connective tissue of the perichondrium often showed fibrillary and mucoid degeneration. The connective tissue cells of the cardiac valves were swollen, resembled cartilage cells and contained blue granules

14. Washington, J. A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 4, chap. 30.

15. de Lange, C.; Gerlings, P. G.; De Kleyn, A., and Lettinga, T. W.: Some Remarks on Gargoylism, Acta pædiat. **31**:398, 1944.

and lipid droplets. The valvular and endocardial connective tissues showed chondroid and mucoid changes. The interstitial connective tissue of the myocardium was increased and was replacing muscle fibers. There was no glycogen in the heart after fixation in dilute solution of formaldehyde U.S.P. for over twenty-four hours. Fibrous thickening was evident in the aortic intima. The connective tissue cells of the media were swollen and contained blue granules; the connective tissue showed a mucoid degeneration. The hepatic lobules were distorted and divided by partitions of connective tissue. The cytoplasm of the hepatic cells was foamy, and the nuclei were eccentric. Lipid infiltration was minimal, but many cells were so high in glycogen (even after partial fixation in dilute solution of formaldehyde U.S.P.) as to suggest to de Lange and associates that hepatomegaly was due mainly to accumulation of glycogen in the parenchymal cells. There was minimal fibrosis of the spleen. Staining with scarlet red, revealed no lipid, but a few black granules were present with the Lorrain Smith-Dietrich stain. The cells of the anterior lobe of the pituitary gland were indistinctly outlined, and the cytoplasm of the majority was almost colorless. The eosinophilic cells were few, but the basophilic cells were normal. There was an apparent decrease in total number of cells, with a diffuse increase in amount of connective tissue.

The epiphysial line of the ulna was irregular, and the adjacent cartilage cells were swollen. Ossification was inactive, and the epiphysial line was occasionally interrupted with foci of fibrous tissue. The bone marrow showed mucoid degeneration. In the cervical portion of the spine, cartilage cells extended into the perichondrium, which showed chondroid changes in its interstitial tissue. Gross microscopic examination of the brain revealed it to be entirely normal. De Lange concluded that these lesions belonged in the gargoylism group, even though a lipid storage process was not demonstrable.

De Lange and co-workers[15] cited several additional pathologic reports on gargoylism which have not been available to us for study. De Lange[16] examined the brain of a typical patient with gargoylism and observed that the nerve cells contained lipid material. Though the staining reactions were different, changes in the cells closely resembled those of juvenile amaurotic familial idiocy. No abnormalities were noted by Hässler in a biopsy specimen of the radius.[17] Kny[18] was able to explain the osteodystrophy of gargoylism by demonstrating growth of hypoplastic bone and cartilaginous alteration. No lipid material was seen in the car-

16. de Lange, C. (1942), cited by de Lange and others.[15]

17. Hässler, F.: Monatschr. f. Kinderh. **80**:271, 1939; Die Beziehungen der Hurlerschen Krankheit (Dysostosis multiplex-dysostotische Idiotie-gargoylisme) zum Kretinismus, ibid. **86**:96, 1941; cited by de Lange and others.[15]

18. Kny, W.: Zur Kenntnis der Dysostosis multiplex Typ Pfaundler-Hurler, Ztschr. f. Kinderh. **63**:366, 1942; cited by de Lange and others.[15]

tilage cells, an observation which differed from the experience of Schmidt.[19] Kny also observed a vacuolated, degenerated liver with incipient cirrhosis. While he saw considerable lipid infiltration of the liver, no hepatic glycogen was present. In the brain, the alteration of the nerve cells with lipid infiltration suggested the identity of amaurotic idiocy and gargoylism.

A recently recorded fatal case was that of Strauss.[20] She described a 3 year old girl who had the characteristic manifestations of gargoylism, and who died suddenly of cardiac failure. Autopsy showed skeletal deformity with dorsolumbar kyphosis, scaphocephaly and shortening and curving of the long bones. Cardiac hypertrophy and nodular thickening of the cardiac valves were also observed. The intima of the aorta and other arteries was thickened. Hepatosplenomegaly was present. Large vacuolated cells were observed in the heart, blood vessels, reticuloendothelial system and skeleton. There was ballooning of the ganglion cells of the central nervous system and of the hepatic parenchymal cells. Strauss discovered by staining that little of the vacuolated intracellular material was lipid in nature. She pointed out that nonlipid material of high molecular weight, such as glycogen, might be the material stored in tissue cells and, furthermore, that there could be an inability of the cells to dispose of these accumulating substances.

Most recent to report on autopsy in a case of gargoylism were Strauss and his co-workers.[21] The patient was a man aged 29 who had presented since childhood a grotesque facial appearance and contraction deformities of the hands and feet. The lymph nodes, lungs and duodenum contained masses of foam cells in which the lipid content did not account for the excessive vacuolization of the cytoplasm. The ganglion cells of the central nervous system were enlarged and contained granular brown pigment. These lesions did not appear to be those of gargoylism, and, furthermore, the typical, common lesions of the disease were not present in this case.

The ocular pathologic lesions in gargoylism were reviewed in this laboratory by Hogan and Cordes.[22] Of the 3 cases they reported,[22a] 2 (cases 3 and 4) are presented in this paper. Corneal clouding was a

19. Schmidt, M. B.: Die anatomischen Veränderungen des Skeletts bei der Hurlerschen Krankheit, Zentralbl. f. allg. Path. u. path. Anat. **79**:113, 1942; cited by de Lange and others.[15]

20. Strauss, L.: A Case of Gargoylism, New York State J. Med. **47**:157, 1947.

21. Straus, R.; Merliss, R., and Reiser, R.: Gargoylism: Review of the Literature and Report of the Sixth Autopsied Case with Chemical Studies, Am. J. Clin. Path. **17**:671, 1947.

22. (*a*) Hogan, M. J., and Cordes, F. C.: Lipochondrodystrophy (Dysostosis Multiplex: Hurler's Disease); Pathologic Changes in the Cornea in Three Cases, Arch. Ophth. **32**:287 (Oct.) 1944. (*b*) Cordes and Hogan.[4a]

characteristic in more than 75 per cent of the recorded cases and was usually present by the third year, although it has been present at birth. The corneas were diffusely hazy, and examination with the slit lamp showed uniformly distributed noncrystalline and only slightly refractile bodies, first occupying the medial and deeper layers of the cornea. Later, the entire cornea was involved, and vision was correspondingly diminished. The histologic studies of the cornea by Hogan and Cordes[22a] confirmed those of Kressler and Aegerter,[13] Berliner[23] and Rochat.[24] Bowman's membrane was partially replaced with large polygonal cells having abundant, granular cytoplasm. There was enlargement of the corneal cells, which showed similar granular cytoplasm. No lipid material was present. The epithelial and endothelial layers of the cornea appeared normal. It was concluded by Hogan and Cordes,[22a] that the corneal opacities resulted from infiltration of phagocytic cells into Bowman's membrane and from swelling of the corneal corpuscles.

THE CELLULAR LESION IN GARGOYLISM

From the pathologic standpoint, the lesions encountered in tissues from our series of cases are similar, if not identical. Unquestionably, gargoylism is a disease of abnormal storage. While the material available to us for study has not been ideal, certain patterns of alteration in tissues and cells are apparent. While only 1 autopsy was complete, representative sections from most of the tissues from the other autopsies and from several surgical biopsies have been examined. Almost all tissues of the body show histologic changes; the signs and symptoms of the disease are readily explained by the extensive storage reaction.

The characteristic cellular lesion is a swelling of the cytoplasm. This results in enlargement of the cell in many instances. The altered cytoplasm varies in different situations. It may be entirely clear and colorless and surrounded merely by a thin cellular membrane. At times, there may be a thin rim of compact cytoplasm surrounding a centrally placed, clear, vacuolated space. This observation is true of the hepatic cells, in which the nucleus is often slightly flattened and displaced by the central vacuole. In still other cells, the cytoplasm superficially appears to have a fine or coarse granularity. The cells involved in this disease have an internal granular structure like that of the cells of a myoblastoma.[25] It is

23. Berliner, M. L.: Lipin Keratitis of Hurler's Syndrome (Gargoylism or Dysostosis Multiplex): Clinical and Pathologic Report, Arch. Ophth. **22**:97 (July) 1939.

24. Rochat, G. F.: The Corneal Changes in Dysostosis Multiplex, Ophthalmologica **103**:253, 1942.

25. (*a*) Howe, C. W., and Warren, S.: Myoblastoma, Surgery **16**:319, 1944. (*b*) Crane, A. R., and Tremblay, R. G.: Myoblastoma (Granular Cell Myoblastoma or Myoblastic Myoma), Am. J. Path. **21**:357, 1945. (*c*) Simon, M. A.: Granular Cell Myoblastoma (Myoblastic Myoma, Rhabdomyoma Granulo-Cellulaire), Am. J. Clin. Path. **17**:302, 1947.

interesting to note that in the neoplastic cells of the myoblastoma, the granular cytoplasm failed to stain for lipid material or glycogen.[25c] The cytoplasm of the cells in gargoylism often closely resembles that of the decidual cells of the endometrial stroma, elements which normally contain abundant glycogen.[26] The grayish blue, granular, vacuolated cytoplasm is a feature of both cells. Red-staining granular material, indicating the presence of carbohydrate, is demonstrable in the cells, both of a myoblastoma and of decidua, with the method using the periodic acid and Schiff's reagent[7] on tissue and fixed in dilute solution of formaldehyde U.S.P.[2] The visible cellular granules in gargoylism, however, often appear with the routine stains as a fragmented network of residual cytoplasm in which there are numerous, tiny, clear, vacuolated spaces. In certain cells, particularly the nerve cells, this altered cytoplasm may be localized to one portion of the cell, with the normal cytoplasmic architecture being preserved in the rest of the cell.

Several sorts of cells are thus altered in this disease. Epithelial cells, particularly those of the liver, are extensively involved in this storage mechanism. Other epithelial elements, for example, the epidermis, the glands of the skin and the anterior lobe of the pituitary gland, are similarly involved. Reticuloendothelial cells, both fixed and wandering, show the same clear swelling of the cytoplasm in many tissues, particularly in the spleen and lymph nodes. Nerve cells of all portions of the nervous system, even enteric autonomic ganglions, show a similar storage reaction in their cytoplasm.

Among the most striking changes were those observed in the mesodermal connective tissues. Fibrocytic cells, chondrocytes and osteocytes showed swelling, enlargement and vacuolization of their cytoplasm. Certainly, this widespread change in connective tissue was probably responsible for the malformations of the skeleton and soft tissues and the diminished growth. Since the intercellular substance supporting these cellular elements is derived from their cytoplasm, and if the latter is altered or replaced by storage of some abnormal material, the intercellular matrix (collagen, osteomucin, or chondromucin) derived from the cells would also be expected to be abnormal. Certainly, in many situations in the cases of our series, these matrixes had an abnormal microscopic appearance. Lack of normal osteoblastic activity, particularly at epiphysial lines, was particularly striking, and, undoubtedly, it was a prominent factor in the greatly retarded skeletal growth. The interruption of the continuity of epiphysial lines by groups of foam cells was also significant in this record.

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26. Dempsey, E. W., and Wislocki, G. B.: Observations on Some Histochemical Reactions in the Human Placenta, with Special Reference to the Significance of the Lipoids, Glycogen and Iron, Endocrinology **35**:409, 1944.

In the cardiac valves, in the coronary arteries and in the vascular endocardium, the storage phenomenon in the fibrocytic cells was associated with increased amounts of altered collagenous, intercellular substance.

Generally, this altered connective tissue had lost its normal fibrillary characteristics and appeared swollen and homogeneous. Osteomucin and chondromucin often appeared poorly formed.

HISTOCHEMICAL STUDIES IN GARGOYLISM

In the fatal cases of gargoylism in which autopsies were recorded in the literature, certain evidence was presented indicating that the syndrome is a lipid storage disease, with complex lipoprotein or phospholipid as the substance deposited in the various tissue cells. It should be noted that de Lange and associates[15] and Strauss[20] suggested that the substance accumulating in the cells in gargoylism might be glycogen.

Study with various histologic stains for lipids in several of our cases revealed small amounts of lipid substances in many of the altered swollen cells. It is, however, apparent that the lipid substance which stains cannot account for the tremendous increase in the volume of cytoplasm of the altered cells. In the liver, for example, the lipid material demonstrated lay at the periphery of the large central unstained vacuole. In the nerve cells, abundant fine lipid droplets were present in the cytoplasm of the cells, but, since the normal lipid content of nerve cells is high, the amount demonstrated was not significant. The lipid droplets may be the result of alteration in the colloid suspension due to storage of the abnormal material. Incidentally, in those nerve cells showing swelling of only a portion of the cytoplasm, there was less lipid substance in the involved part of the cell, suggesting that the normal lipid was displaced or diluted by the other substance. The possibility, therefore, that the stored substance is a lipid, even a complex one, seems remote.

The substance causing swelling and vacuolization of the tissue cells usually cannot be stained consistently with a variety of the common protein stains, either acidophilic or basophilic, and is therefore presumably not purely protein in nature. Exceptions to this statement were the presence of violet granules in the altered corneal connective tissue cells when stained with cresyl violet and the presence of blue granules in hepatic cells when stained with toluidine blue and thionine. In some instances the altered cellular cytoplasm stained a pale grayish blue color with hematoxylin, particularly after fixation in alcohol. These reactions are characteristic of mucoproteins.[8] Furthermore, this basophilic staining reaction with hematoxylin was more intense in frozen sections than in paraffin sections and was also more intense in tissues fixed in dilute

solution of formaldehyde saturated with calcium salicylate. Hueper[27] pointed out that pectin, a macromolecular carbohydrate substance, combines with calcium salts to form water-insoluble calcium pectinate and that pectin stains cherry red with ruthenium red. However, in 1 of our fatal cases, hepatic tissue embedded in both pyroxylin and paraffin failed to stain with ruthenium red.

One of the complex carbohydrates susceptible to a staining reaction is glycogen, which stains with Best's carmine[5] and with the Feulgen-Bauer technic.[6] Fixation of the tissue in absolute alcohol or similar nonaqueous materials has been considered until recently to be essential for the demonstration of glycogen in histologic sections. In the material from 8 autopsies, tissue fixed in alcohol was available for study in only 2. Glycogen was present, however, in the liver in small amounts in several of the fatal cases in tissues fixed in dilute solution of formaldehyde U.S.P., but the amount present did not account for the excessive vacuolization of the hepatic cellular cytoplasm. It may have been present in larger quantities at death, probably disappearing subsequently by postmortem glycolysis.

In 2 cases (7 and 8) in which tissues had been fixed in absolute alcohol and in Carnoy's fixative, glycogen was generally demonstrable by staining neither with Best's carmine[5] nor by the Feulgen-Bauer method.[6] In these 2 cases, the interval between death and autopsy was forty hours and seventeen and a half hours, respectively, intervals long enough for postmortem glycolysis to occur.

In a surgical biopsy of an epiphysial cartilage of a fibula (case 9), the cartilage cells were crowded with eosinophilic granules staining with Best's carmine. These granules, presumably glycogen, accounted for the cellular enlargement, and the amount of glycogen present was greatly in excess of the normal amount of glycogen found in cartilage cells. This tissue had been decalcified in 5 per cent nitric acid in absolute alcohol before embedment in pyroxylin.

In biopsy specimens of the liver and a costal cartilage (case 10) fixed in the solution of dioxane, trinitrophenol, formaldehyde and acetic acid described previously, abundant intracellular glycogen was demonstrated by the Feulgen-Bauer method.[6] With the use of similarly fixed hepatic tissue from a case of true glycogenosis (von Gierke's disease) as a control, incubation of hepatic sections from both cases with saliva resulted in loss of the granular material staining with the Feulgen-Bauer method. This indicates that the carbohydrate stored in the hepatic cells in gargoylism is a polysaccharide, presumably glycogen, rather than a less complex carbohydrate. When hepatic tissue from the same case was fixed in Carnoy's solution, it was of interest that little glycogen could be demonstrated with the Feulgen-Bauer method. When treated, however, with the solution of

27. Hueper, W. C.: Macromolecular Substances as Pathogenic Agents, Arch. Path. 33:267 (Feb.) 1942.

dioxane, trinitrophenol, formaldehyde and acetic acid, glycogen could be stained readily. The amylase of saliva also acted on this preparation to prevent the staining of glycogen.

Since the solution of dioxane, trinitrophenol, formaldehyde and acetic acid is strongly acidic, the possibility exists that the glycogen may be combined in some instances with a protein, as a glycoprotein or mucoprotein. This would account for the basophilic staining of the cytoplasm of the altered cells in several of the cases. The appearance of glycogen in tissues fixed in Carnoy's solution only after treatment with the solution of dioxane, trinitrophenol, formaldehyde and acetic acid may be the result of acid hydrolysis of a glycoprotein. Replacement of the dioxane solution with tenth-normal hydrochloric acid did not give the same staining reaction. In 1 case, the glycogen was readily stained with Best's carmine, after the tissue had been decalcified with 5 per cent nitric acid in absolute alcohol. It is probable, therefore, that treatment with tenth-normal hydrochloric acid not only caused disassociation of the glycogen-protein complex but also resulted in further acid hydrolysis of the carbohydrate. The failure of the trinitrophenol and acetic acid solution and of the 5 per cent nitric acid solution similarly to affect the glycogen by hydrolysis, even though the protein and glycogen were disassociated, may be explained by the fact that these two acids were in nonaqueous solutions; hence they were not in an ionized form.[28]

The intracellular glycogen or glycoprotein in the liver and cartilage cells (when demonstrable) was present in quantities sufficient to account for the cellular enlargement. It is likely that similar appropriate histochemical study of the other tissues involved in gargoylism will also reveal widespread intracellular storage of a glycoprotein.

HEREDITARY ASPECTS OF GARGOYLISM

While gargoylism may have a familial occurrence, there is evidence from our series of cases indicating that a maternal influence does not operate as an etiologic agent. In 2 of our cases of gargoylism, a twin brother and sister were not affected. In both instances, the twins were of the double ovum variety, in the first case indicated by the dissimilar sexes of the twins, and in the second case by the fact that there were two placentas, fused only by the fetal membranes. Although the manifestations of the disease appear early in life, it seems that the process is inherent in the child rather than being secondary to a pathologic process in the mother. If the latter were true, one would expect twin individuals even of a dissimilar type to be affected by the disease process.

If we assume that the abnormal granular substance in the leukocytes is the same material present in the tissue cells, and the evidence suggests

28. Hassid, W. Z.: Personal communication to the authors.

that it is, the sequence of events in 1 of our cases suggests that the unknown substance is present in tissue cells from an early period in life. In this instance, abnormal granules in the neutrophilic leukocytes were observed when the patient was 10 months of age, about one year before the disease was otherwise manifested. In another case in our group, the corneas were opaque from birth. It is not until later that the material accumulates in large enough quantities to alter the normal growth of the skeletal and other structures. An early fetus, a sibling of 1 of our patients (case 5) did not demonstrate the histologic changes of the disease. In the case reported by Ashby, Stewart and Watkin,[12] the patient had a repulsive appearance at birth; the skull was deformed, and there was a film over both eyes. Mental development was retarded. These observations indicate that clinical evidence of the disease may be present at birth or early in life.

Familial recurrence in the same generation was noted in 5 of our 13 families with gargoylism. In our group of cases, there has been no history of the disease occurring in previous generations. Boecker[29] cited an instance with familial recurrence, in which, in line of descent from 1 woman, there were 1 boy with dysostosis multiplex in the second generation, a girl with eccentro-osteochondrodysplasia (Morquio's disease) and 2 boys with dysostosis multiplex in the third generation, and a boy with dysostosis multiplex in the fourth generation.

Halperin and Curtis[30] discussed the genetic aspects of gargoylism, and expressed the opinion that the disease is due most likely to the action of a single recessive autosomal gene.

Abramson and Kurtz[31] reviewed the instances of familial recurrence of glycogenosis and suggested its inheritance as a mendelian recessive character. These authors recorded 4 cases of glycogenosis occurring in siblings.

LEUKOCYTES IN GARGOYLISM

Reilly[32] previously described abnormal granules in the leukocytes in gargoylism. In 4 of 8 cases studied, he observed numerous, large, dark violet granules in the cytoplasm of the leukocytes, which were more numerous in the neutrophilic leukocytes than in lymphocytes or monocytes. The granules were not refractile and did not resemble eosinophilic

29. Boecker, E.: Zur Erblichkeit der Dysostosis Multiplex, Ztschr. f. Kinderh. **63**:688, 1943.

30. Halperin, S. L., and Curtis, G. M.: The Genetics of Gargoylism, Am. J. Ment. Deficiency **46**:298, 1942.

31. Abramson, H., and Kurtz, L. D.: Familial Glycogen Disease: Report of Four Fatal Cases of the Hepatic Form of the Disease in Siblings of One Family, Am. J. Dis. Child. **72**:510 (Nov.) 1946.

32. Reilly, W. A.: The Granules in the Leukocytes in Gargoylism, Am. J. Dis. Child. **62**:489 (Sept.) 1941.

or toxic granules. They varied in size from fine dustlike to large coarse particles. Usually, 60 to 90 per cent of the neutrophilic leukocytes and 20 to 25 per cent of the total white blood cells contained these granules, though the percentage of cells containing them fluctuated widely. These altered cells were observed in smears from aspirated bone marrow and splenic tissue in several cases.

Dried blood films from 4 of our recent cases were available for further study and review. With Wright's stain, all the neutrophilic leukocytes contained many large granules in their cytoplasm. These were larger and more numerous and uniform than toxic granules. They stained dark pink to violet with the Wright stain. Between these granules were normal, smaller neutrophilic granules. The abnormal granules were present in smaller numbers in the monocytes but were not encountered in the lymphatic cells of the blood. These granules did not stain with congo red after fixation in methyl alcohol. After fixation with absolute ethyl alcohol, followed by immersion in water, they did not stain with Wright's stain. They did not stain with scarlet red. After fixation with absolute ethyl alcohol, blood films were covered with a thin layer of pyroxylin and stained with Best's carmine; these smears showed faint pink, indistinct granules in the cytoplasm of the neutrophilic leukocytes, suggesting the presence of glycogen. Normal blood films stained by the same method as a control showed no pink staining of the leukocytic cytoplasm. With the method using periodic acid and Schiff's reagent,[7] the neutrophilic leukocytes had bright pink, finely granular cytoplasm. Only a few faint pink granules were observed in the monocytes, and there were none in the lymphocytes. Normal blood films used as a control for the staining method showed distinctly less intense and nongranular eosinophilic staining of the neutrophilic leukocytic cytoplasm.

Bridge and Holt[33] concluded from their studies that all the glycogen in the blood in glycogenosis could be accounted for by glycogen storage in the leukocytes. Recently, it was shown[34] that the concentration of glycogen in isolated leukocytes in glycogenosis is 2.7 to 7.4 times higher than in normal leukocytes. However, in 2 of our recent cases of glycogenosis, no abnormal granules were seen in the leukocytes, and there was no staining of the leukocytic cytoplasm with glycogen stains (Best's carmine and periodic acid-Schiff's reagent method).[2]

RELATION OF GARGOYLISM TO OTHER MACROMOLECULAR SYNDROMES

Hueper[27] reviewed the pathogenic aspects of macromolecular substances and pointed out the similarities between the experimental lesions

33. Bridge, E. M., and Holt, L. E., Jr.: Glycogen Storage Disease: Observations on the Pathologic Physiology of Two Cases of the Hepatic Form of the Disease, J. Pediat. **27**:279, 1945.

34. Wagner, R.: Glycogen Content of Isolated White Blood Cells in Glycogen Storage Disease, Am. J. Dis. Child. **73**:559 (May) 1947.

and those of diseases in which known endogenous macromolecular substances are stored in tissue cells. A wide variety of macromolecular compounds, synthetic or biogenic, may produce similar physiologic or tissue changes. Combinations of basic macromolecular substances occur, forming lipoproteins, glycoproteins and glycolipids. In general, tissue cells are not able to dispose of these stored macromolecular materials, since they are relatively inert and only degraded slowly over a long period of time. By altering vascular permeability, these substances escape into intercellular spaces and are stored there, as well as in intracellular situations.

Hueper[27] further reviewed and compared the organic lesions resulting from both exogenous and endogenous macromolecular storage. In glycogenosis (von Gierke's disease) swelling and distention of nerve cells in the brain and spinal cord due to storage of glycogen were observed.[35] Staining of glycogen in the white matter of the cerebral hemispheres was noted, and perivascular deposits of glycogen were abundant.[35] Mason and Anderson[36] observed pink staining of anterior horn nerve cells in the spinal cord and of the glial cells of the central nervous system with Best's carmine in glycogenosis. In juvenile amaurotic familial idiocy and Niemann-Pick disease, similar changes in nerve cells resulted from lipid storage in these cells.[27] Comparable alteration in nerve and ganglion cells is seen after prolonged administration of polyvinyl alcohol. All these instances of alterations in nerve cells are similar to those of gargoylism.

It was shown by Hueper[27] that certain changes in the blood, designated by him as the macromolecular hematologic syndrome, occur both in experimental macromolecular storage and in human storage diseases. These changes include anemia, reduction of hemoglobin, leukopenia or leukocytosis, increase in conglutination and sedimentation of erythrocytes, delayed coagulation, thrombopenia, hemorrhagic phenomenon and decreased fibrinogen and globulin. Some of these features were noted in gargoylism.[1]

While gross skeletal lesions do not ordinarily occur in glycogenosis, Krakower[37] described microscopic changes in 2 cases. Zones of arrest of growth were seen adjacent to the epiphyses, and the cartilaginous columns were often penetrated by vascularized marrow. Some of the bony trabeculae of shafts showed irregular absorption. Vacuolization and enlargement of the nuclei of the cartilage cells was present, and in the marrow spaces were numerous, large, pale, vacuolated histiocytic cells. These changes are suggestive of those in gargoylism. As in similar cells in the

35. Kimmelstiel, P.: Ueber Glykogenose, Beitr. z. path. Anat. z. allg. Path. **91**:1, 1933.

36. Mason, H. H., and Anderson, D. H.: Glycogen Disease, Am. J. Dis. Child. **61**:795 (April) 1941.

37. Krakower, C.: The Lipoid Factor in Glycogen Storage Disease, J. Pediat. **9**:728, 1936.

splenic pulp, neither glycogen nor lipid material could be demonstrated. In the marrow in Niemann-Pick disease and Gaucher's lipidoses are numerous foamy reticulum cells storing lipid substance. In our cases of gargoylism, macrophages with foamy cytoplasm were encountered in the bone marrow. Exogenous introduction of macromolecular materials, especially pectin, is followed by foam cell storage in the bone marrow.

The storage phenomena in hepatic cells in glycogenosis, in lipid storage diseases of the Niemann-Pick type, in exogenous experimental macromolecular storage disease and in gargoylism are remarkably similar. The cells are enlarged and their cytoplasm foamy. In gargoylism and glycogenosis, there is often a distinct perilobular cirrhosis which is not unlike that seen in the long-standing fatty liver of alcoholism. Hepatomegaly is present in both glycogenosis and gargoylism, and the hepatic parenchymal cells are enlarged with a delicate granular and vesicular cytoplasm. In glycogenosis, the hepatic cells have been described as "plant-like."[33] In each disease, the amount of lipid material in the cytoplasm does not account for the excessive distention of the cell.

Other pathologic features of glycogenosis include glycogen storage with glycogen casts in the renal tubular epithelium, vacuolated, non-lipid-containing macrophages in pulmonary alveoli and an osteoporotic, easily fractured skeleton.[38]

The lesions of the respiratory tract in gargoylism resemble those in the other storage diseases. Interstitial and intra-alveolar foam cells are seen in polyvinylosis and methylcellulosis. In Niemann-Pick disease, cells filled with lipid are seen in similar situations.[27] In gargoylism, foamy macrophages are present in many alveolar spaces; the storage reaction may be related to or may cause the chronic, recurrent infections of the respiratory tract in persons with gargoylism. The striking alteration in the bronchial cartilage, as well as in the other cartilages of the respiratory tract, is apparently comparable with the changes in bronchial cartilage seen in glycogenosis, in which these cartilage cells are loaded with glycogen granules.[36]

Alopecia has been observed in glycogenosis and in dogs with polyvinylosis.[27] In the latter, the injected substance lies in cell groups surrounding hair follicles, suggesting interference with nutrition of the hair follicles. The same lesion has been observed in gargoylism. We have noted partial alopecia of the scalp in several of our cases of gargoylism. The epithelial cells of the surface of the mucosa and skin, as well as of hair follicles and sweat glands, have shown vacuolization indicating storage. In case 7, excessive amounts of glycogen were present in the squamous epithelial cells of the tongue. The skin is often thickened to palpation, and micro-

38. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, in Christian, H. A.: Oxford Loose-Leaf Medicine, New York, Oxford University Press, 1940, vol. 4, pt. 2, p. 214 (229).

scopically the connective tissue cells and fibers are altered by the storage reaction.

In glycogenosis, cardiac involvement occurs. This is characterized by excessive storage of glycogen in myocardial fibers, with secondary cellular degenerative changes leading to cardiac failure. Glycogen accumulation in the walls of arteries and veins has been described.[27] In glycogenosis of the heart, Haymond and Giordano[39] described fibrous subintimal thickening of small coronary vessels. The myocardial fibrous proliferation, presumably associated with glycogen storage, resembled that seen in the endocardium in gargoylism. In exogenous macromolecular disease produced by methyl cellulose or polyvinyl alcohol, Hueper[27] observed atherosclerotic and arteriocalcinotic lesions identical with those of lipid atheromatosis. Administration of acacia to both dogs and children produced aortic intimal thickening. In our group of persons with gargoylism examined at autopsy, all showed comparable vascular lesions, exhibiting a storage reaction in connective tissue cells of the endocardium, valves, coronary and pancreatic arteries and aorta. Cardiac signs and symptoms are common in gargoylism.[1] In 1 of our patients with gargoylism, the cardiac alteration caused death from cardiac failure at 11 years of age. There was cardiac hypertrophy in each case autopsied, varying from 10 to 75 Gm. above the normal average weight for the age.[40]

Renal involvement in exogenous macromolecular disease produced with polyvinyl alcohol, methyl cellulose, acacia or pectin consists of storage of the injected material in the capillary endothelium of glomerular tufts leading to capillary obliteration. In our cases of gargoylism, the storage phenomenon appeared to be present in the glomerular situation, often associated with thickening of the glomerular basement membrane. In exogenous macromolecular disease (polyvinyl alcohol, methyl cellulose and acacia) the renal tubular epithelium is often vacuolated and in glycogenosis, glycogen is often found in the tubular epithelial cells. A similar nonlipid vacuolization was observed in these tubular cells in gargoylism. Injected macromolecular substances often infiltrated the interstitial tissue of the kidney and produced a myxomatous structure,[27] reminiscent of the altered connective tissue in the renal and other interstitial tissues in gargoylism.

In the reticuloendothelial tissue apart from the bone marrow, exogenous macromolecular substances are stored with regularity in phagocytic cells in the spleen, lymph nodes and liver. Almost all the reticuloendothelial cells in gargoylism show apparent similar storage of the un-

39. Haymond, J. L., and Giordano, A. S.: Glycogen-Storage Disease of the Heart, Am. J. Clin. Path. **16**:651, 1946.

40. Farber, S.: The Postmortem Examination, Springfield, Ill., Charles C Thomas, Publisher, 1937.

known substance. The reticuloendothelial system is not a storage site of carbohydrate in glycogenosis, however.

Foam cells in alveoli and the interstitial spaces of the lung are a feature of a lipidosis (Niemann-Pick disease), polyvinylosis and methyl cellulosis.[27] While this lesion does not occur in glycogenosis, it is prominent in most cases of gargoylism. In the latter disease, the same cellular alteration of cartilage cells is seen in and about the bronchi as in the skeleton. Mason and Anderson[36] described excessive glycogen storage in these cells in glycogenosis.

Hueper[27] summarized storage in endocrine glands in both exogenous and endogenous macromolecular disease. Polyvinyl alcohol, pectin, and acacia accumulate in the adrenal gland, and the picture is comparable to the storage reaction in hypercholesteremic xanthomatosis and Niemann-Pick and Gaucher's diseases.[27] Polyvinyl alcohol is deposited in the thyroid gland and interstitial cells of the testes. Endocrine involvement does not occur in glycogenosis. In gargoylism, storage in the endocrine system is a distinct feature of the disease, particularly in the pituitary gland and the interstitial cells of the testes. The storage must interfere with endocrine secretion and may account in part for the retarded skeletal development. Distinct storage was also evident in the thymus and thyroid glands and in the medullas of the adrenal gland.

Corneal alteration is a frequent lesion in gargoylism, occurring in 14 of 18 cases in our series.[1] The corneal clouding and diminution of vision are progressive. Punctate refractile bodies are seen throughout the cornea with the slit lamp,[4a] and histologic studies showed distention of the corneal connective tissue and endothelial cells, due presumably to the storage phenomenon. Prolonged intravenous administration of methyl cellulose in rabbits produced distinct diffuse corneal clouding in 3 of 12 animals.[2] Externally, the corneal opacity closely resembled that of the patients with gargoylism, but examination with the slit lamp in 2 animals (Dr. M. J. Hogan) showed refractile material both in the corneal epithelium and in the outer third of the corneal fibers. This substance, apparently deposited methyl cellulose, appeared as a linear, felted network of refractile fibers. In at least one other macromolecular syndrome, hypercholesteremia, corneal opacity was described.[41] In this instance, deposition of cholesterol occurred in both the corneal connective tissue and the epithelial cells.

The foregoing review indicates the close resemblance of the pathologic lesions of gargoylism to those of the other macromolecular storage diseases, including both experimental disease and the various lipid and carbohydrate storage syndromes occurring in the human being.

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41. Davidson, A.: Primary Lipid Dystrophy of the Cornea, Arch. Ophth. 37:433 (April) 1947.

RELATION OF GARGOYLISM TO MORQUIO'S DISEASE

Skeletal changes of Morquio's disease and gargoylism show many similarities and many distinct differences. Though autopsy has been made on only 1 person with Morquio's disease, 2 skeletal biopsies have been described. Of the changes described in the paper of Einhorn and others,[42] degeneration of the chondrocytes, deficient cancellous and cortical bone and absence of osteoblastic proliferation have been seen by us in the skeletal system of patients with gargoylism. In the biopsy specimen described by Shelling,[43] the shaft showed only mild osteoporosis. In the epiphysial region, the cartilage was disordered and poorly calcified, and the line of ossification was defective. There were porosis and thinning of the marrow trabeculae, which often contained incarcerated cartilaginous masses. These masses had an irregularly striated matrix, and the cells were varied in appearance. Some were vacuolated, and others had shrunken nuclei. Shelling concluded that epiphysial growth was arrested. In both these reports, the skeletal changes described are similar to those of gargoylism. Washington[14] was of the opinion that Morquio's disease and gargoylism were similar if not identical diseases. A recent paper by Einhorn and others[44] recorded observations of the only autopsy made to date on a patient with Morquio's disease. Loss and degeneration of the majority of chondrocytes, with vacuolated foci in the interstitial tissue of the articular cartilages, was described. Subchondral bone was deficient, irregular and poorly trabeculated; there was no osteoblastic or osteoclastic activity. The hepatic parenchyma was described as showing "edema and fatty degeneration," but other lesions suggestive of gargoylism were not described.

CARBOHYDRATE METABOLISM IN GARGOYLISM

While the present evidence indicates that gargoylism represents an abnormal storage disease of a complex carbohydrate, presumably glycogen or glycoprotein, none of the laboratory data obtained to date in this disease explain the physiologic mechanism of the excessive storage of the carbohydrate substance. In a classification of glycogen disease, Mason and Anderson[36] separated by clinical and pathologic data the reported cases into five groups. Group 1 included glycogenosis of the liver (von Gierke's disease) which, in their opinion, was due to a congeni-

42. Einhorn, N. H.; Moore, J. R.; Ostrum, H. W., and Rowntree, L. G.: Osteochondrodystrophia Deformans (Morquio's Disease), Am. J. Dis. Child. **61**: 776 (April) 1941.

43. Shelling, D. H., in Brennemann, J.: Practice of Pediatrics Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 4, chap. 29.

44. Einhorn, N. H.; Moore, J. R., and Rowntree, L. G.: Osteochondrodystrophia Deformans (Morquio's Disease): Observations at Autopsy in One Case, Am. J. Dis. Child. **72**:536 (Nov.) 1946.

tal defect of the hepatic enzymatic system converting glucose to glycogen and glycogen to glucose. When the first mechanism was defective, the dextrose tolerance curve was elevated and prolonged, and the levulose and galactose tolerance curves were normal or low. Group 2 consisted of those cases showing glycogen storage disease of the heart and muscles. Here the congenital carbohydrate conversion defect was thought to be the same, but these patients showed a normal blood glucose response to epinephrine. The patients in group 3 showed hepatomegaly and galactosuria early in life. The defective hepatic enzymatic system was thought to be the one converting galactose to glycogen. Group 4 included instances of excessive secretion of insulin or excessive ingestion of carbohydrate, producing increased amounts of hepatic glycogen. Response to epinephrine was normal, and the liver was able to convert glycogen to glucose in vitro. In group 5 were cases which could not be classified in groups 1 to 4, and in which the data were incomplete. There was hepatomegaly with excessive amounts of glycogen and often a distinct cirrhosis. In some cases, the conversion of glycogen to glucose in vitro was normal. Tolerance curves after ingestion of galactose and dextrose were often high and prolonged. A normal response to epinephrine suggested that the glycogenolytic enzyme system of the liver was normal.

In our series of persons with gargoylism, reducing substances were never found in the urine. Carbohydrate tolerance tests were done in 6 of the patients reported on in this paper. In 2 patients results of oral dextrose tolerance tests were normal. In 1 patient, results of intravenous glucose and galactose tolerance tests and an insulin tolerance test were within normal limits. In another 2 patients, oral galactose tests showed no abnormal retention in 1. The last patient studied (case 10) showed normal curves for levulose and glucose. The blood galactose was 12 mg. per hundred cubic centimeters at the end of two and of three hours after ingestion, an abnormal result which may be explained by structural alteration of the hepatic cells, without postulating a defect in a hepatic enzyme. In this patient, blood glucose curves after administration of insulin and epinephrine were normal.

In the cases of gargoylism recorded in the literature, the status of carbohydrate metabolism has not been generally investigated. De Lange and her co-workers[15] described an abnormal galactose tolerance test in their case. After ingestion of 40 Gm. of galactose, the blood galactose was above 40 mg. per hundred cubic centimeters, and there was prolonged excretion.

It seems apparent from the present evidence that the carbohydrate storage mechanism of gargoylism represents a different metabolic disorder from that of true glycogenosis. There are some similarities between the laboratory data obtained in gargoylism and those obtained in some of the

cases of glycogen storage disease described by Mason and Anderson[36] which were placed in their group 5. The excessive cellular carbohydrate in gargoylism may be metabolically inactive and may not be involved in the turnover of an otherwise normal carbohydrate metabolism. Its apparent combination with protein as a glycoprotein supports this thesis.

SUMMARY AND CONCLUSIONS

1. Gargoylism is a disease of early childhood, characterized by striking gross and microscopic alterations in almost all tissues of the body.

2. The basic lesion is the intracellular and extracellular deposition and storage of a substance giving the histochemical reactions for glycogen.

3. Certain histochemical data presented suggest that the glycogen may be combined with protein.

4. Laboratory studies indicate that glycogen storage process in gargoylism is not associated with demonstrable alteration in carbohydrate metabolism, as in true glycogenosis (von Gierke's disease).

5. Widespread involvement of most tissues, including the nervous, cardiovascular, reticuloendothelial, endocrine, skeletal and other systems, explains the protean clinical manifestations of the disease.

6. The lesions of gargoylism are similar to or identical with some of those of the other macromolecular storage diseases of both endogenous and exogenous origin.

7. Further, more precise, histochemical, chemical and enzymatic studies on the material stored in the tissues are indicated. Combination of glycogen with a protein stored in the cytoplasm of the cells may explain the inconsistent histochemical staining reactions recorded to date.

Parnassus and Third Avenues (22).

The staff of the Sonoma State Home, Eldridge, Calif., cooperated in this study.

EXPERIMENTAL TOXOPLASMOSIS

I. Transmission of the Infection in Utero and Through the Milk of Lactating Female Mice

HEINZ EICHENWALD, B.A.
NEW YORK

THE PROTOZOON toxoplasma has long been known to be pathogenic to a large variety of mammals and birds,[1] but interest in the organism was aroused only when Wolf, Cowen, and Paige[2] firmly established that the parasite causes a disease in human infants. Pinkerton and Weinman[3] subsequently showed that not only infants but also adults can have toxoplasmosis, a disease marked by variable clinical and subclinical manifestations. In very young children and babies, hydrocephalus, microcephaly, chorioretinitis, cerebral calcifications and psychomotor disturbances are observed most commonly,[4] while in older children acute, nonsuppurative encephalitis is also seen.[5] Relatively few cases of the disease in adults have been reported. A spotted-fever-like syndrome associated with atypical pneumonia appears to be the cardinal sign of the acute disease,[6] while chorioretinitis is probably a manifestation of a more

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

1. (*a*) Nicolle, C., and Manceaux, L.: Sur une infection à corps de Leishman (ou organismes voisins) du gondi, Compt. rend. Acad. d. sc. **147**:763-766, 1908. (*b*) Splendore, A.: Un nuovo protozoa parassita de conigli, Rev. Soc. sc., São Paulo **3**:109-112, 1908. (*c*) Wenyon, C. M.: Protozoology: A Manual for Medical Men, Veterinarians, and Zoologists, New York, William Wood & Company, 1936. (*d*) Manwell, R. D., and Herman, C.: Blood Parasites of Birds of the Syracuse, New York, Region, J. Parasitol. **21**:415 (Oct.) 1935.

2. Wolf, A.; Cowen, D., and Paige, B. H.: Human Toxoplasmosis: Occurrence in Infants as Encephalomyelitis, Science **89**:226-227 (March 10) 1939.

3. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940.

4. Cowen, D.; Wolf, A., and Paige, B. H.: Toxoplasmic Encephalomyelitis: IV. Clinical Diagnosis of Infantile or Congenital Toxoplasmosis, Arch. Neurol. & Psychiat. **48**:689-793 (Nov.) 1942.

5. Sabin, A. B.: Toxoplasmosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1943.

6. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: Previously Unrecognized Disease Entity Simulating Typhus-Spotted Fever Group, J.A.M.A. **116**:807-814 (March 1) 1941.

chronic course.[7] There is now a considerable body of evidence to indicate that, in addition to the more acute disease, a latent or subclinical infection can occur in man. Such chronic, asymptomatic toxoplasmosis was experimentally produced in mice by Weinman[8] and has been demonstrated to occur naturally in wild rats.[9]

It is now generally accepted that only one species of Toxoplasma exists. Sabin[10] found that organisms isolated from different hosts (*a*) cross immunize, (*b*) are morphologically indistinguishable and (*c*) can be successfully inoculated into every host reported so far to be susceptible to the infection. These facts suggested to Sabin[5] that the reservoir of infection existing in a large variety of lower animals is of considerable importance in the little known epidemiology of the disease. At present, few concrete facts have been established concerning the transmission of the organism from host to host; these can be summarized as follows:

With man, the only natural proved method of transmission is the congenital transfer of the protozoon from mother to fetus in utero. Mothers of such infected children show no signs of illness and appear to suffer no ill effects from the presence of the toxoplasma in their tissues; with the infant, on the other hand, the infection often terminates fatally.[11] A similar congenital transmission of the disease has been demonstrated experimentally in mice,[8] but the incidence of infection among the off-spring was very low.

Insect vectors have been postulated, but attempts to transmit the disease by this route have been uniformly unsuccessful.[12]

Sabin and Olitsky[13] have shown that mice are susceptible to infection via the alimentary tract if fed food containing viable toxoplasmas. If mice are allowed to starve until they become cannibalistic and are then permitted to devour an infected mouse, toxoplasmosis will result in most of them. It is thus possible that omnivores and carnivores can become infected in nature by the ingestion of tissue harboring the parasite.

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8. Weinman, D.: Chronic Toxoplasmosis, J. Infect. Dis. **73**:85-92 (July-Aug.) 1943.

9. Perrin, T. L.; Brigham, C. D., and Pickens, E. G.: Toxoplasmosis in Wild Rats, J. Infect. Dis. **72**:91-96 (Jan.-Feb.) 1943.

10. Sabin, A. B.: Biological and Immunological Identity of Toxoplasma of Animal and Human Origin, Proc. Soc. Exper. Biol. & Med. **41**:75-80 (May) 1939.

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12. Chatton, E., and Blanc, G.: Notes et réflexions sur le toxoplasme et la toxoplasmose du gondi, Arch. Inst. Pasteur de Tunis **10**:1-40 (July) 1917.

13. Sabin, A. B., and Olitsky, P. K.: Toxoplasma and Obligate Intracellular Parasitism, Science **85**:336-339 (April 2) 1937.

Since transmission of the disease via the alimentary tract is possible, it appeared profitable to examine the possibility that the milk of lactating, infected mothers could serve as a vehicle for the transfer of the organism from mother to offspring.

EXPERIMENTAL INVESTIGATION

The Toxoplasma strain used throughout this investigation is of human origin, having been isolated originally by Dr. A. B. Sabin and maintained since then in mice.[14]

I transferred the organisms routinely in mice for over a year by intraperitoneal inoculation of ascitic fluid or of liver emulsion. Transfers were made regularly every three or four days. When obtained originally from the Harvard Medical School, the strain showed considerable affinity for the central nervous system, but after long-continued serial passage through the animals became so adapted to liver, lung, spleen, intestinal mucosa, kidney and heart tissue that even after subcutaneous inoculation most organisms became concentrated in these visceral organs, with only small and infrequent foci of infection occurring in nerve tissue. The disease in these mice was accompanied with acute pulmonary congestion, with edema as its principal sign. Hepatic and myocardial lesions were also severe, and the meninges were occasionally invaded. The picture presented thus resembles to some degree acute adult toxoplasmosis.

As Weinman[8] has shown, mice fed or given injections of suitably small quantities of infected material do not succumb to the disease but there develops, after generalized parasitemia, a chronic infection without evident illness. Many of the animals used in this study continued to harbor organisms in pseudocysts distributed only in the lung, heart and spleen for about three months after the initial generalized systemic infection. Weinman, on the other hand, observed surviving pseudocysts mostly in the brain, where they persisted sometimes for over nine months without provoking any reaction in the surrounding tissue. This difference in the site of location of the pseudocysts is most probably due to the different tissue affinities exhibited by Weinman's strain and the one used in this study. Since immune reactions are at their lowest level in the brain, it is logical that pseudocysts will persist longest there.[8]

TRANSMISSION OF TOXOPLASMA BY MOTHERS IN ACTIVE STAGE OF THE DISEASE

Thirty-five healthy 3 month old virgin female mice were caged separately and fed a diet consisting of standard mouse food "purina." Their intake was restricted to an amount that would keep the animals hungry without any visible

14. The Toxoplasma strain was obtained through Prof. D. L. Augustine, of the Harvard Medical School.

sign of undernutrition.[15] After five days, healthy adult male mice were introduced into each of the cages and the animals allowed to mate. The appearance of a vaginal plug in the female was taken as an indication of successful copulation, a method which has proved reliable.[16] As soon as a vaginal plug was noted in one of the animals, the male was removed from the cage. On the seventh day after copulation, each of 20 females was fed a small amount (about 0.2 Gm.) of toxoplasma-infected mouse liver; 15 control females were given a similar amount of liver from healthy mice. This method of infecting the animals was chosen because (*a*) it probably resembles natural conditions more closely than injection and (*b*) because this dose of infected material had previously been found to produce regularly a nonfatal generalized infection within five to eight days, lasting a minimum of three weeks and followed by a chronic carrier state of several months' duration.

After having ingested the liver, the mice were allowed to feed ad libitum for the remainder of the experiment.

Thirty of the animals proved to be pregnant and gave birth to their litters seventeen to twenty days after fertilization. The mothers and their litters were divided immediately into four groups:

Group A: Five infected lactating mice, each nursing 5 of their own young
Group B: Ten infected lactating mice, each nursing 5 young born of healthy mothers
Group C: Five healthy lactating mice, each nursing 5 young born of infected mothers
Group D: Five healthy lactating mice, each nursing 5 of their own young

(Whenever it was necessary to remove a litter from the mother and transfer it to a foster mother, this was done within an hour after birth.)

It can readily be seen that the litters included in group A were exposed both to intrauterine and to milk-borne infection, while those of group B were exposed only to the latter. Group C was included to give an indication of the incidence of congenital infection. Group D represents the controls.

The young were allowed to remain with the females until weaned (about eighteen days); then they were caged separately and fed ground "purina" pellets. Any animal that died during the experimental period was examined at once for the presence of toxoplasmas, both microscopically and by inoculation of organ emulsions into healthy mice. Twenty-five days after birth, all surviving members of the various litters and all mothers were killed and examined in the same manner for the presence of the protozoon. All mothers fed infected liver were found to harbor toxoplasmas, while those given normal liver showed no sign of infection. The results are shown in table 1.

The high incidence of infection in group B strongly suggests the existence of milk-borne transmission of the toxoplasma; however, the possibility that the organisms may have been transmitted to the offspring by other routes must also be considered. The following experiment was, therefore, performed:

15. This was done so that the animals would readily eat the infected material given later; the slight degree of malnutrition has no influence on the course of infection.

16. Snell, G. D.: Biology of the Laboratory Mouse, Philadelphia, The Blakiston Company, 1941.

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An apparatus for the collection of milk from lactating mice was devised which consisted essentially of a sterile, small-bored, rubber-tipped medicine dropper. By placing the open tip of the glass tube over a nipple and gently massaging while suction was applied with a rubber bulb, milk could fairly readily be collected. Previous to every milking, the ventral surface of each mouse was carefully scrubbed with 70 per cent alcohol in order to eliminate any possible contaminating material.

TABLE 1—*Experimental Toxoplasmosis in Four Groups of Lactating Mice*

Group	Description of Group	Total No. of Young	No. of Young Dying of Toxoplasmosis up to Age of 25 Days	Average Survival Period of Mice Dying During Experiment, Days	No. of Young Surviving but Found Infected at Age of 25 Days	No. of Young Found not Infected	Total Percentage of Young Infected
A	Five infected lactating mice, each nursing 5 of their own young	25	10	7±3	3	12	52
B	Ten infected lactating mice, each nursing 5 young born of healthy mothers	50	4	16±2	8	38*	24
C	Five healthy lactating mice, each nursing 5 young born of infected mothers	25	7	4±2	2	16	36
D (controls)	Five healthy lactating mice, each nursing 5 of their own young	25	0	—	0	25	—

*The total includes 2 mice which died during the experimental period of causes other than toxoplasmosis.

TABLE 2.—*Milk-Borne Transmission of Toxoplasma in Young Mice*

Group	Description of Group	Total No. of Young	No. of Young Dying of Toxoplasmosis up to Age of 25 Days	Survival Period of Mice Dying During Experiment, Days	No. of Young Surviving but Found Infected at Age of 25 Days	No. of Young Not Infected	Total Percentage of Young Infected
1	Young fed indirectly with milk from 5 infected lactating females	20	2	16, 18	2	16	20
2	Young fed indirectly with milk from 3 healthy lactating females	10	0	—	0	10	0

Fifteen lactating mice infected during pregnancy in the same manner as those in the previous experiment were milked once or twice daily. The milk obtained was promptly fed to 20 suckling mice born of healthy mothers. The feeding was best accomplished by inserting the open tip of the milking device into their mouths and forcing the milk out of the tube by gradually compressing the rubber bulb. Between these one or two daily feedings, the young mice were permitted

to obtain additional nourishment directly from 5 healthy lactating females. Ten normal suckling mice which received similar artificial feeding with milk from 3 healthy donors were included in these groups as controls.

Artificial feeding of the test mice was continued for ten days; then they were allowed to obtain all their nourishment from their healthy foster mothers until weaned. Mice dying during the course of the experiment were tested for the presence of toxoplasma as before, and all survivors, controls and the 5 healthy foster mothers were killed twenty-five days after birth of the young and similarly examined. None of the foster mothers were found to be infected. The other results are shown on table 2.

Substantially the same incidence of infection was obtained whether the litter was in direct contact with the infected foster mother or was fed indirectly with her milk. After birth, therefore, transmission of the disease by routes other than by milk would not appear to be an important factor.

Logically enough, the incidence of the disease is highest among those offspring in which both infection of the fetus in utero and infection of the young by milk is possible. A comparison of the results in groups B and C in table 1 shows that prenatal transmission of the toxoplasma occurs more readily than transmission through milk. However, a temporal reltationship must be considered here. It is quite conceivable that if the mother became infected late in pregnancy the number of young acquiring the disease in utero would be small and, conversely, that infection of the mother earlier, or just before pregnancy, would give a higher percentage of intrauterine infection.

It should be noted that deaths among congenitally infected mice not only were more frequent but occurred sooner than among mice infected through milk. At autopsy, a much more diffuse and heavier parasitization was observed in the animals infected in utero; no organ, including the central nervous system, escaped invasion by the toxoplasma. On the other hand, with milk-infected animals, the digestive tract, liver, spleen and lungs were parasitized almost exclusively, and a much smaller number of organisms was present.

TRANSMISSION OF TOXOPLASMA BY MOTHERS IN THE CHRONIC CARRIER STAGE OF THE INFECTION

Fifteen female mice which were shown to be capable of transmitting toxoplasma to their offspring congenitally as well as through their milk under the conditions of the previous experiment (i.e., in the active stage of the disease) were allowed to mate again with healthy males forty to sixty days after they had been infected initially. The litters, totaling 75 animals, were permitted to obtain milk from their own mothers. The survivors and the mothers were killed ten days after weaning and examined for the presence of toxoplasmas by the same procedures as be-

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fore. Two of the young mice died during the course of the experiment but failed to show any evidence of toxoplasmosis. None of the survivors were found to harbor any organisms, although 11 of the mothers (73 per cent) were still carrying parasites in their viscera. As pointed out before, in these chronic carriers the organisms are confined within fairly sparsely distributed pseudocysts, observed mostly in the lung, heart and spleen, and there is little or no tissue reaction. The toxoplasmas are thus effectively "bottled up;" they are unable to enter the general circulation, and thereby to give rise to secondary foci in the uterus, mammary glands and other organs from which they had previously been eliminated by immune reactions. An interesting phenomenon thus exists whereby pseudocyst formation in a few specific organs both protects the toxoplasma from the immune reactions of the host and the host with its offspring from the destructive action of the toxoplasma. That such a balance can be maintained permanently is doubtful. Weinman[8] found an unexpectedly short life span in his chronic carrier mice, while under the conditions of the present study the host succeeded in eliminating the parasites in about three months. Thus, either the host or the parasite can eventually gain the ascendancy.

Considering all these factors, it was not surprising that when pregnant chronic carriers unable to transmit the disease to their offspring were given intravenous injections of 0.05 cc. of ascitic fluid containing viable toxoplasmas, 5 of the 50 mice divided into ten litters became infected in utero. Likewise, organisms once more appeared in the milk if the injection was made during or, at most, a few days before lactation. Substantially the same results were obtained by feeding large quantities of infected liver (1.0 to 1.5 Gm). The effect of these heavy doses was the production of a transient parasitemia, since more organisms were introduced than the immune reactions of the host could effectively handle. Within a few days, however, balance was again restored. The parasitemia, nevertheless, lasted sufficiently long to allow the toxoplasmas to reach the uterus and mammary glands and thus lead to infection of the offspring. Preliminary evidence indicates that only a small degree of immunity to the disease is transmitted from the mother to the litter in utero through the placenta, but further work on this problem is necessary.

NATURE OF THE TOXOPLASMA FOUND IN MILK

There is no evidence to lead one to suppose that the organisms transmitted by milk differ from the forms usually encountered in tissue fluids. All facts indicate that the number of toxoplasmas in milk is small; extensive microscopic examination of preparations stained by the Giemsa method revealed only a few organisms. They were morphologically indistinguishable from those found in ascitic fluid, and their resistance to

physical agents was likewise about the same: At 3 C. milk remained infective up to eight days; infectivity was lost in fifteen minutes at 50 C. and in ten minutes at 54 C.

Infected milk is capable of producing toxoplasmosis when administered to mice either parenterally or orally.

COMMENT

It would be unwise to apply unselectively data obtained by animal experimentation to human disease. However, as Weinman[8] stated, "it is important to note that thus far the correspondence of the human and the experimental disease (toxoplasmosis) in mice is extraordinarily complete." In addition, it should be pointed out that a "fresh" strain of toxoplasma may not necessarily behave like the adapted, viscerotropic strain used in these experiments. There is undoubtedly considerable variation in behavior among different strains. With these facts in mind, the following points may be of interest to the clinician:

1. A new route of transmission of the toxoplasma from mother to child must be considered; the infant may escape intrauterine infection, but if breast fed may subsequently be infected. It follows that if the mother acquires the disease after pregnancy but during lactation, infection of the breast-fed infant is still possible. The statement that the child is in danger only if the mother harbors the organisms during pregnancy may, in the light of evidence presented here, require modification.

2. The possibility that the symptoms of the disease produced by ingestion of toxoplasmas may be different from those observed in cases of the congenital disease must be considered. These symptoms would, of course, not be evident at birth but would be noted later. Unless a very large number of organisms are ingested, a chronic, rather than an acute, form of the disease would most likely tend to occur, since human resistance is probably fairly high. Both intrauterine and milk-borne infection may be involved in some cases. Infants born with signs of toxoplasmosis should, therefore, not be breast fed by the mother.

3. These results suggest the possibility of human infection through ingestion of milk from infected cows or goats. There are no data on the incidence of toxoplasmosis in these animals, although they are known to be susceptible;[17] definite information would be valuable. The labile nature of the organism would seem to indicate that such a route of transmission is not a common occurrence. Pasteurization would, of course, serve to render milk noninfective.

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17. Olafson, P., and Monlux, W.: Toxoplasma Infection in Animals, Cornell Vet. **37**:179-190 (Jan.) 1942.

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4. The fact that female mice can transmit the disease to their offspring in utero or through milk only while an active, generalized infection is in progress, rather than in the chronic carrier state, may have some bearing on the observation that in a large majority of known cases in human infants one sibling alone was infected, while the others showed no sign of present or past toxoplasmosis and gave negative serologic reactions.

SUMMARY

Experimental evidence is presented to show that in mice transmission of toxoplasmosis to the offspring via the milk of infected mothers is possible. This route of transmission exists in addition to a previously recognized one, namely, infection of the fetus in utero.

As compared in the congenitally acquired disease, fewer organisms are observed in the tissue of milk-infected mice, and the distribution of the parasites is more limited. These factors result in a relatively milder disease.

Congenital or milk-borne transmission occurs probably only while the mother is undergoing an active, generalized infection. Chronic carriers rarely, if ever, are capable of transmitting the organisms to their offspring, except when they are reinfected with heavy doses of toxoplasmas during pregnancy. The resulting parasitemia is of relatively short duration in these immune animals.

Methods of transmission from mother to offspring other than through milk do not play a significant role after birth, as judged from these experiments.

The toxoplasmas found in milk are morphologically indistinguishable from those occurring in other tissue fluids and possesses the same resistance to physical agents.

The application of these observations to the human disease is discussed.

505 East Sixty-Eighth Street.

Case Reports

THROMBOSIS OF THE VENA CAVA AND HEPATIC VEINS (CHIARI'S SYNDROME) IN A PATIENT WITH NEPHROSIS

Report of a Case and Observation on Serum Phosphatase and Prothrombin Time of Plasma

KATHARINE DODD, M.D.
RALPH J. JOHANSMANN, M.D.
AND
S. RAPOPORT, M.D., Ph.D.
CINCINNATI

A CASE of Chiari's syndrome is reported, with autopsy and observations on the serum phosphatase level and the prothrombin time of the plasma.

REPORT OF CASE

M. T., a 3½ year old white boy, was admitted to the Children's Hospital on June 2, 1945, with a history of a "cold" followed by swelling of the face and extremities, oliguria and anorexia. Examination revealed generalized edema and a moderate amount of fluid in the peritoneal cavity. The blood pressure was 98 mm. of mercury systolic and 60 mm. diastolic. The nonprotein nitrogen of the serum measured 34 mg., the total protein 3.8 Gm. and the albumin 1.5 Gm., per hundred cubic centimeters. The serum cholesterol was 572 mg. per hundred cubic centimeters one month after admission and 1,088 mg. two weeks later. His urine contained albumin, a few white blood cells and granular casts. A diagnosis of lipid nephrosis (nephrotic syndrome) was made. Except for short visits home, he remained in the hospital until his death, on July 6, 1946. During the entire period results of analyses of his urine remained practically unchanged except for a few red blood cells observed at intervals. The nonprotein nitrogen of the serum usually ranged from 35 to 50 mg. per hundred cubic centimeters. The blood pressure rose slightly at times but was usually within normal limits. The serum protein was always low; the albumin was often less than 1 Gm. per hundred cubic centimeters. The temperature reached 99 to 100 F. almost every day; occasionally it rose to 101 or 102 F.

He gained weight steadily during the first few weeks in the hospital, and by August 1, two months after admission, so much fluid had accumulated in the peritoneal cavity that abdominal paracentesis was necessary for relief of the distention. During the remaining eleven months of his life sixteen more abdominal paracenteses were performed. By September 6 it was noted that the superficial veins over the lower part of the chest and the upper portion of the abdomen were becoming prominent. No acute episode of fever, vomiting or abdominal pain

From the Children's Hospital Research Foundation and the Departments of Pediatrics and Pathology, University of Cincinnati College of Medicine.

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had occurred. The venous distention increased steadily until his death, but it was not until June 1946 that enlargement of the liver was noted. At that time the liver was found to extend 2½ fingerbreadths below the costal margin. The edge felt firm and the surface slightly nodular.

There was an unexplained episode of slight jaundice in October 1945. Another brief episode of jaundice occurred in January 1946 after a reaction to transfusion with fever.

By December 1945 the patient began to complain of abdominal pain and vomited occasionally. In April 1946 it seemed certain that portal obstruction must have occurred. Although the legs and abdomen were always greatly swollen, the face and arms appeared free of edema, and even emaciated. The veins were greatly dilated on the chest and abdomen and were visible over the neck, the back and both inguinal regions, the inner aspect of the thighs and the ankles. During the first few days of April the child became irritable, cried a great deal, complained of pain in the abdomen and vomited several times. He was capricious about his food and demanded salt constantly. The patient then contracted measles, modified by the administration of human immune globulin U.S.P. He had Koplik spots and slight fever, but no rash. He was sent to the hospital for contagious diseases. After this episode he seemed weaker, but he did not vomit or complain of any pain for some time.

In June 1946, while at home, the patient suddenly began to vomit all food and drink, and diarrhea developed. Since he was dehydrated when readmitted to the hospital, an intravenous infusion was given. The dehydration and the diarrhea were promptly relieved. With improvement in hydration the abdomen rapidly filled with fluid, and another paracentesis became necessary on July 2. Severe vomiting recurred; his condition rapidly deteriorated, and he was discovered cold and almost pulseless on July 6. He died before fluid therapy could be started.

Laboratory Studies.—The cephalin flocculation test gave a 3 plus reaction in October and a negative reaction in November; it again gave a 3 plus reaction in June and a 4 plus reaction on the day of death, in July. During the first episode of jaundice the total serum bilirubin was 3.2 mg. per hundred cubic centimeters, of which 1.1 mg. gave a direct reaction. During the second episode of jaundice the bilirubin was 4.2 mg. per hundred cubic centimeters, all of which reacted indirectly.

In October the value for serum phosphatase was 4 Bodansky units. On April 4, during the episode of abdominal pain, it was 85 Bodansky units; the value had fallen to 65 units by April 9, to 35 units on April 18 and to 15 units on June 24.

The nonprotein nitrogen level generally ranged from 35 to 50 mg. per hundred cubic centimeters. On April 4 it rose to 97 mg. It was still 87 mg. on April 9 and reached 64 mg. on April 18, but gradually fell to 36 mg. per hundred cubic centimeters. On the sample obtained on the patient's readmission to the hospital, in June 1946, the nonprotein nitrogen measured 42 mg. per hundred cubic centimeters. It was 127 mg. in a sample obtained immediately after death. The value for inorganic phosphorus was normal at all times; the cholesterol was always increased and measured 853 mg. per hundred cubic centimeters at the time of death.

Prothrombin times were obtained only during the first episode of jaundice. In the first sample, the prothrombin time of the undiluted plasma was prolonged to 30.0 seconds (by the method using Russell viper venom, the normal mean value is 19.9 seconds, with a standard deviation of 1.2 seconds); the dilution constant, expressing the increase in seconds per unit increment of reciprocal dilution, was 0.3 second (the normal mean value is 3.8 seconds, with a standard deviation of 0.8 second). Another sample taken two weeks later gave a clotting time of 19.4 seconds

for undiluted plasma and a dilution constant of 0.9 second. A further test in the middle of November showed a clotting time of 23.2 seconds for the undiluted plasma, with a dilution constant of —0.3 second; that is, plasma dilution up to a 1:5 clotted more rapidly than the undiluted plasma.

Necropsy Report.—Gross Examination: Numerous large, dilated, blue veins were visible in the skin of the neck, the anterior portion of the chest, the upper part of the abdomen and the back, and over the inguinal regions, the inner surfaces of the thighs and the ankles. The inferior vena cava was distended and occluded by a firm, dark red and yellow, laminated thrombus, which was adherent to the intimal surface and extended from the level of the renal veins into the right atrium. The renal veins, bilaterally, and the right hepatic vein also were filled with a similar thrombus. A firm, dry thrombus, which was composed principally of dark red, clotted blood, distended and occluded the portal vein and its mesenteric tributaries. This thrombus was laminated in portions and was firmly adherent to the

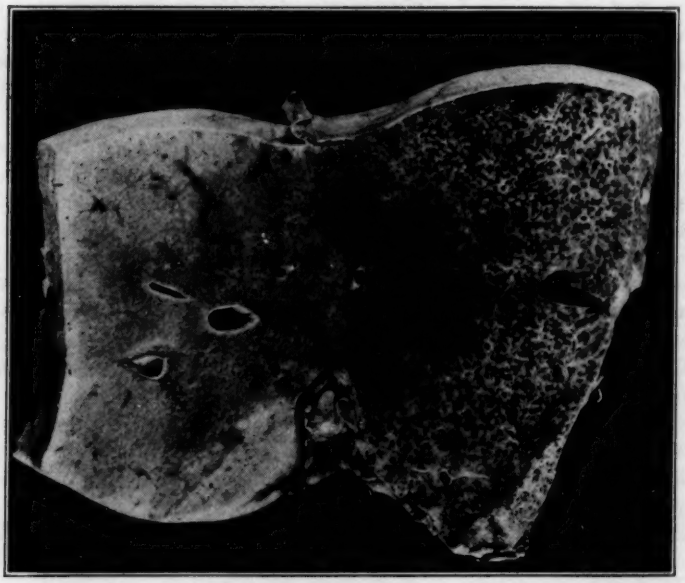

Fig. 1.—Cross section of the liver showing the relatively noncongested left lobe and the extremely congested right lobe, with thrombosis of the hepatic veins.

intima of the vessel just below the point of entrance of the splenic vein. It extended to, but not into, the large intrahepatic radicles of the portal vein and at this site was detached easily from the wall of the vessel. The splenic vein also was filled with, but not distended by, a soft clot of blood, which had retracted slightly from the wall of the vessel. The peritoneal cavity contained approximately 300 cc. of slightly turbid fluid. The surfaces of the peritoneum were congested, and there was moderate fibrous thickening of the parietal portion.

The liver was slightly enlarged and weighed 615 Gm. The smooth capsular surface was dark red over the right and caudate lobes and light tan over the left lobe. The cut surface of the right and caudate lobes revealed light yellow tissue, mottled with prominent dark red markings, which imparted to it a nutmeg appearance. Numerous large veins in these lobes were thrombosed. The left lobe was

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pale yellowish tan, with only slight evidence of congestion. A sharp line of demarcation existed between the congested and the relatively noncongested portions of the liver. The gallbladder was normal.

The spleen, approximately two to three times normal size, weighed 108 Gm. and was composed of a dark red, moderately soft pulp.

There were no esophageal varices and no abnormalities of the gastroenteric tract except for moderate congestion of the small intestine.

The kidneys were about twice normal size and together weighed 215 Gm. The capsules were thin, and the external surfaces were smooth. The swollen cortices were mottled with light yellowish tan and reddened areas. The medullas were moderately congested. The calyxes, pelves, ureters and urinary bladder were normal.

The heart was of average weight but slightly increased in size. The chambers on the right side were dilated, and a pale yellowish pink thrombus, extending from the inferior vena cava, hung in the right atrium.

The lungs appeared normal, and no free fluid was present in the pleural cavities.

Microscopic Examination: Some of the veins emerging at the hilus of the kidneys had a slight lymphocytic reaction throughout all the layers of their walls and contained organized and recanalized thrombi. Other veins, with similar signs of inflammation, were distended by more recently formed thrombi, which were only beginning to be organized in their peripheral zones. Some of the veins appeared normal.

Only a slight and patchy inflammatory reaction, consisting chiefly of lymphocytes, was present in the intima and media of the inferior vena cava. The vessel was occluded by a thrombus, which was well organized in the outer zone but unorganized in the central zone.

The pathologic changes in the liver consisted of pronounced chronic passive congestion in the right lobe, with central necrosis, and early portal cirrhosis throughout all lobes. In the right lobe there were degeneration, necrosis and even absence of hepatic cords in the central portions of the lobules. The central veins and sinusoids were distended with blood, and the framework was relatively increased in amount. The peripheral portion of the hepatic lobules was fairly well preserved, there being only slight fatty infiltration of some of the hepatic cells. However, the sinusoids in the peripheral portion were moderately congested, and the Kupffer cells were slightly swollen. Several of the larger hepatic veins of the right lobe contained thrombi, in which organization was less advanced than in the thrombus of the inferior vena cava. None of the smaller hepatic veins or the interlobular branches of the portal vein were thrombosed. In the left lobe, the central veins and the sinusoids of the central portion of the lobules were distended with blood, and there was attenuation of some of the hepatic cords. None of the extensive degenerative changes present in the right lobe were seen. In the portal areas of all lobes there was a cellular inflammatory reaction, composed chiefly of lymphocytes, with fewer histiocytes and eosinophils, and accompanied with an increase in connective tissue and slight proliferation of the bile ducts.

The media and, to a greater extent, the adventitia of the splenic vein were infiltrated with lymphocytes, histiocytes and eosinophils. A thin layer of organized thrombus was adherent to the intimal surface. Overlying this layer was a fresh thrombus, the central portion of which consisted of a postmortem clot.

The mesenteric veins were distended with unorganized thrombi. Inflammatory reaction in these veins was slight.

There were degeneration and karyorrhexis of the central portions of the splenic follicles. The sinusoids of the pulp were distended and engorged with

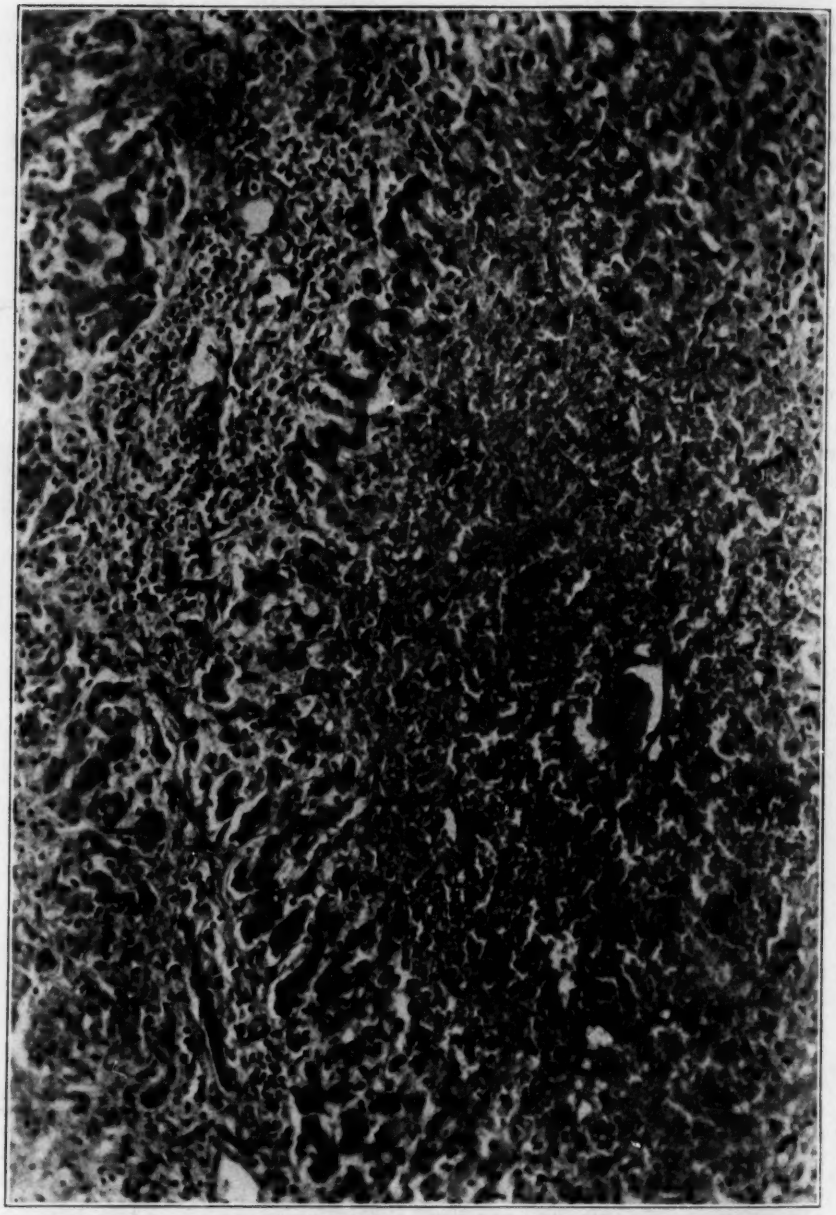

Fig. 2.—Microscopic appearance of a representative lobule of the right lobe of the liver. There are conspicuous congestion of the sinusoids and necrosis and disappearance of the hepatic cords in the central and middle zones. Lymphocytic infiltration, fibrosis and reduplication of bile ducts are evident in the portal canals.

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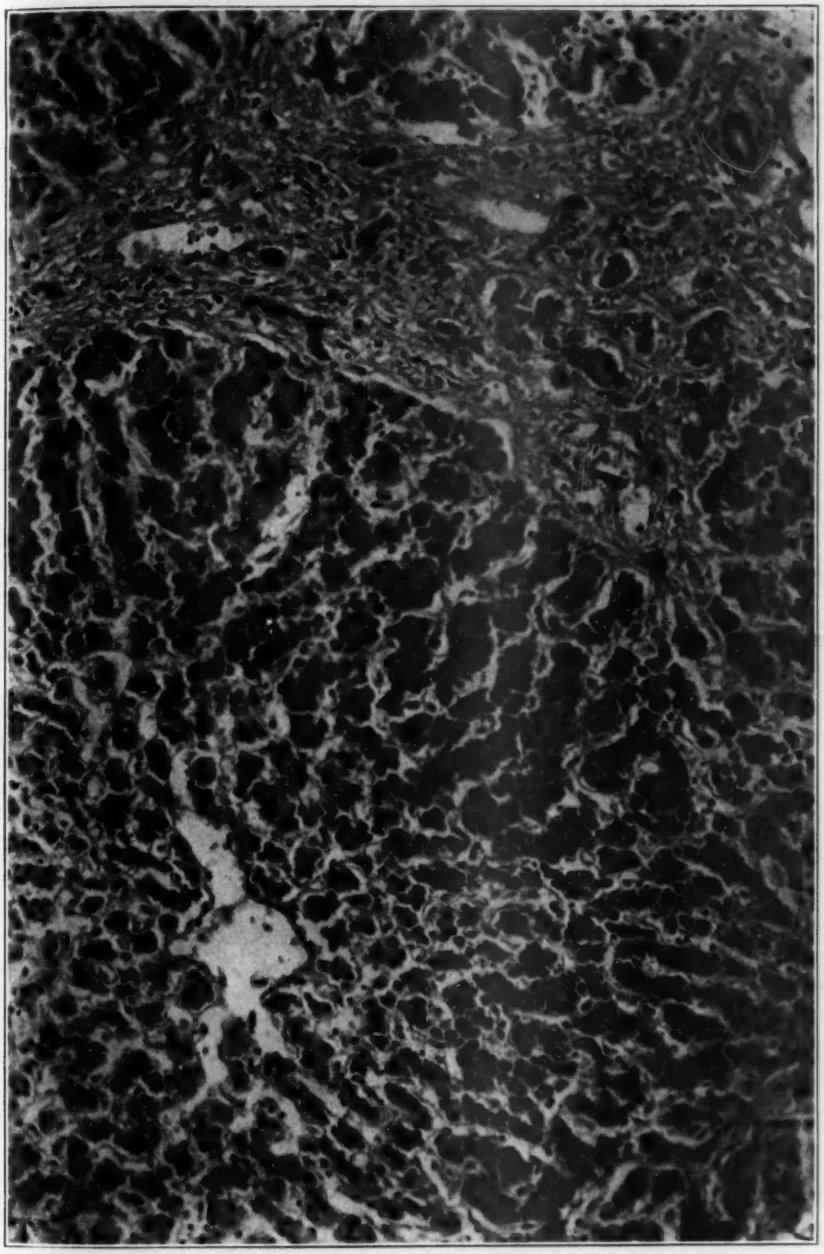

Fig. 3.—Microscopic appearance of a representative lobule of the left lobe of the liver. The sinusoids draining into the central veins are slightly dilated; the hepatic cords are essentially normal and portal cirrhosis is evident.

Fig. 4.—Microscopic appearance of a well organized thrombus in a small vein of a renal hilus.

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blood, and there was a moderate amount of blood pigment in the reticuloendothelial cells of the pulp. There were no thrombi.

The pathologic changes in the kidney were characteristic of the nephrotic syndrome. Whereas many glomeruli appeared normal, some showed slight endothelial proliferation and thickening of the capillary basement membrane, which were best demonstrated in sections prepared with Mallory's aniline blue stain. Some capsular membranes were adherent to the glomeruli with obliteration of the subcapsular space. A few glomeruli were completely hyalinized. Many of the convoluted tubules were distended and filled with precipitate, and most of them were lined with a swollen, granular epithelium, filled with tiny vacuoles. In many areas where glomeruli showed evidence of glomerulitis there was atrophy of the convoluted tubules, accompanied with inflammatory reaction and fibrosis in the interstitial tissue. The small arteries and arterioles appeared normal. The small veins were moderately congested.

COMMENT

This case is an example of a rare and little understood pathologic entity, thrombosis of the hepatic veins. By 1945 about 70 instances of this condition, which is known as Chiari's syndrome, had been reported in the literature.[1] In the majority of cases, as in the present one, local thrombosis of the vena cava was present. The etiology of the syndrome is obscure. The condition may occur alone or in association with other disorders. Of these disorders, primary polycythemia, cirrhosis, infections and neoplasms of the liver are the most frequent.

Only 7 cases of the syndrome in children[2] have been reported. The disease in each instance was insidious in onset. Abdominal distention, ascites and dilatation of the superficial veins over the upper part of the abdomen and the chest wall were noted, and usually some degree of edema of the legs was seen. Jaundice was not observed. The symptoms were indefinite, but in every instance the occurrence of abdominal pain and vomiting during the course of the disease was described. One patient died of carcinoma of the liver at least twenty-three years after the onset of his illness. The other patients died three months to four years after the occurrence of symptoms, apparently of chronic obstruction of the hepatic veins. The thrombosis in each child appeared to be a primary occurrence and not a complication of another disorder, such as has often been described in adults. Extensive thrombosis of the vena cava was not present in any of the children.

Although Chiari's syndrome in a patient with nephrosis has not previously been reported, thrombosis of blood vessels has been noted as a complication of the disease. Two of 9 patients of Aldrich[3] on whom postmortem examinations were made had thrombi, 1 of the renal vein and the other of the iliac veins. Both children died with infection of the

1. Kelsey, M. P., and Comfort, M. W.: Occlusion of Hepatic Veins: Review of Twenty Cases, Arch. Int. Med. **75**:175-183 (March) 1945. Hirsh, H. L., and Manchester, B.: Chiari's Syndrome, New England J. Med. **235**:507-511 (Oct. 3) 1946.

2. Hutchison, R., and Levy Simpson, S.: Occlusion of Hepatic Veins with Cirrhosis of Liver, Arch. Dis. Childhood **5**:167-186 (June) 1930.

3. Aldrich, C. A.: Nephritis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 3, chap. 28, p. 24.

blood stream. The thrombosis was ascribed to sepsis. Schwarz and Kohn[4] discovered thrombosis of the right middle cerebral artery in 1 of 9 children who died with nephrosis. The other 8 patients had peritonitis, but no mention was made of infection in the child with thrombosis. No evidence of sepsis was present in the patient reported on here. He was given prophylactic sulfonamide medication throughout his illness.

The question arises whether in patients with nephrosis a tendency to thrombosis may be related to derangements in the humoral balance, more specifically, to changes in the composition of the plasma.

The prothrombin time of patients with nephrosis is characterized by a greatly decreased dilution constant, an expression of a reduced slope of the dilution curve, whereas the clotting time of the undiluted plasma is variable. The data on 6 patients with nephrosis, including the 1 reported on here, are summarized in the table and illustrate the point. It may be seen that the prothrombin time ranged beyond the normal

Prothrombin Time in the Plasma of Patients with Nephrosis

Case No.	Plasma Prothrombin Time	
	Undiluted Plasma,* Seconds	Dilution Constant,* Seconds
1	30.0 19.4 23.2	0.3 0.9 —0.3
2	18.3 19.9 19.8 17.6	2.3 0.6 1.3 1.4
3	22.5 14.1 20.6 23.4	0.4 1.0 2.4 1.2
4	20.1 22.8	1.4 2.4
5	20.8	2.0
6	18.3	1.7

*The mean normal value of undiluted plasma is 19.9 seconds, with a standard deviation of 1.2 seconds; that of the dilution constant is 3.8 seconds with a standard deviation of 0.8 second.

limits in both directions but that the dilution constant was always less than normal. The plasma in case 1 showed wider fluctuation of the prothrombin time and perhaps greater reduction in the dilution constant than that of any other patient. It is regrettable that no samples of plasma were examined during the latter period of his illness.

The interpretation of the behavior of plasma in nephrosis is hypothetic as yet. It is thought that the reduced slope of the dilution curve, with the correspondingly short clotting time of plasma dilutions, is an expression of an increased prothrombin content of the plasma, which is masked to a variable extent in undiluted plasma by the presence of clot-

4. Schwarz, H., and Kohn, J. L.: Lipoid Nephrosis: A Clinical and Pathologic Study Based on Fifteen Years' Observation, with Special Reference to Prognosis, Am. J. Dis. Child. **49**:579-593 (March) 1935.

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ting inhibitors. According to an alternate hypothesis, the observations may be explained by the activity of accelerators which, supposedly, is increased in diluted plasma, while the underlying prothrombin level varies widely. Such a hypothesis is less in keeping with the known behavior of secondary factors affecting the clotting mechanism, factors which in general are more active in undiluted than in diluted plasma. One would also have to assume a completely erratic behavior of the prothrombin level in nephrosis, varying from extreme hypoprothrombinemia to hyperprothrombinemia.

As to the character of secondary factors influencing the prothrombin time, the possible role of alterations in the distribution of plasma proteins may be mentioned. Among these variations, a great increase in the plasma fibrinogen, which sometimes exceeds 1 Gm. per hundred cubic centimeters, is prominent. A portion of the globulins, that belonging to the β-globulins, is likewise increased, while other proteins, albumin in particular, are greatly diminished. The relation of these changes to the mechanism of clotting is obscure. There is no indication that an increase in plasma fibrinogen per se can affect the prothrombin time. Another factor, equally undetermined, with a possible effect on the clotting mechanism may be related to the great increase in lipid constituents of the plasma of patients with nephrosis.

The frequency of the changes in the prothrombin time as compared with the rarity of published reports on the incidence of thrombosis in patients with nephrosis may indicate that other factors, about which it would be idle to speculate, are of determining importance in the development of the tendency to thrombosis.

The changes in the phosphatase level observed in this patient appear of theoretic, as well as of practical, interest. At present there is considerable uncertainty as to the mechanism and the significance of increases in serum phosphatase in hepatic disease. According to one point of view, the liver is concerned only with the excretion of the serum phosphatase via the biliary passages; consequently, to proponents of this theory, increase in serum phosphatase in itself signifies biliary obstruction. According to another view, hepatic cells are capable of producing phosphatase. Increase in phosphatase, while of greater extent in persons with obstructive lesions, is thought to represent a specific response of hepatic cells to injury. The great increase in phosphatase, exceeding 85 Bodansky units, in our patient, in whom the hepatic veins of one portion of the liver only were occluded, without any evidence of biliary obstruction, would appear as strong evidence for the view that hepatic cells may respond to certain stimuli with production of phosphatase.

SUMMARY

A case of thrombosis of the vena cava and hepatic veins (Chiari's syndrome) in a child with nephrosis is reported. Thrombi were also present in the renal veins and in the portal area. Great increase in the serum phosphatase occurred in the course of the disease. Observations on the prothrombin time of 6 patients with nephrosis are recorded. The clotting time of undiluted plasma was observed to be variable, but the slope of the dilution curve was always reduced.

Elland and Bethesda Avenues.

ABSENCE OF TRANSVERSE AORTIC ARCH WITH DEFECTS OF CARDIAC SEPTUMS

Report of a Case Simulating Acute Abdominal Disease in a Newborn Infant

DONALD WEISMAN, M.D.
AND
H. D. KESTEN, M.D.
WHITE PLAINS, N. Y.

COMPLETE interruption of the arch of the aorta is a rarer condition than narrowing of an otherwise normally developed vessel. Accurate evaluation of the older literature is difficult because of frequent lack of sharp differentiation between, on the one hand, complete loss of continuity along the arch and, on the other, mere narrowing or even atresia with a cordlike vestige remaining. Abbott[1] emphasized that complete disappearance of part of the aortic arch may happen in one of two sites: (*a*) in the descending arch between the orifice of the left subclavian artery and the entrance of the ductus arteriosus, which vessel forms the descending aorta, this type being merely an extreme form of the infantile variety of coarctation and (*b*) much more rarely, in the transverse arch just after the origin of the left common carotid and before that of the left subclavian artery, which vessel is given off from the descending arch of the aorta with no connection between the latter and the transverse arch. In 1927, Abbott found 2 cases of the latter type in the literature, the first reported by Greig in 1852. In 1936,[2] she presented another example in which the hypoplastic aorta ended after giving off the innominate and left common carotid arteries, while the pulmonary artery with bicuspid valves formed the descending arch via a widely dilated ductus arteriosus. The heart also contained a persistent ostium atrioventriculare commune, with atresia of the mitral ring. The infant survived fifteen hours.

The four instances of "descending aorta given off by the pulmonary artery" referred to by Peacock[3] in 1866 do not qualify in the group under discussion, since in each of them a small channel connected the ascending arch with the descending aorta. Herxheimer (1910)[4] stated that 8 cases

From the White Plains Hospital, and the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York.

1. Abbott, M., in Osler, W.: Modern Medicine: Its Theory and Practice, ed. 3, revised and re-edited by T. McCrae, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 793.

2. Abbott, M.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p. 50.

3. Peacock, T.: On Malformations of the Human Heart, London, J. Churchill & Sons, 1866, p. 150.

4. Herxheimer, G., in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere: Ein Hand- und Lehrbuch für Morphologen, Physiologen, praktische Aerzte und Studierende, Jena, G. Fischer, 1910, pt. 3, no. 3, sect. 2, chap. 4.

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of complete absence of the aortic arch were in the literature, the earliest being Steidele's in 1818, and added 1 of his own, but Hamburger[5] by critical study reduced this number by at least 2. Which of the remaining cases exhibited interruption at the isthmus (Abbott's group *a*) and which higher in the arch (the rarer group *b*) cannot be determined, since most of these old reports are unavailable for study. Hamburger found only 1 example of a defect of group *b* type in 15,000 autopsies at Johns Hopkins Hospital. In this case the heart had an associated transposition of the great vessels. Evans[6] described 3 cases of complete interruption of the aortic arch, 1 at the isthmus, the other 2 above this level, so that the left or both subclavian arteries arose from the portion of the trunk which included the distal pulmonary artery and the descending aorta.

The current case of this evidently rare congenital malformation of the aortic arch appears to be unique, as fas as can be judged from the available literature, in that the interruption of the aorta occurred proximal to the left common carotid artery, as well as to the left subclavian, both these vessels arising from the entirely separate portion of the trunk of the pulmonary artery and the descending aorta. This arrangement of vessels, together with defects of the interauricular and interventricular septums, led to a misleading clinical picture of acute intra-abdominal disease.

REPORT OF CASE

Clinical Findings.—J. P., a white boy, was born at term by cesarean section and weighed 2,600 Gm. Respirations commenced spontaneously. The color of the skin was normal until the first feeding, following which cyanosis was noted, but this was relieved by suction. Urine and meconium were passed in usual amounts during the first two days. Approximately forty-eight hours after birth the child became weak and limp and began to regurgitate feedings. Physical examination disclosed cyanotic lips and nail beds with mottled areas of cutaneous pallor. The temperature was normal. The lungs were clear. The heart sounds were regular and of good quality, and no murmurs were heard. The abdomen was distended and tense, and the liver appeared to be large. The extremities were normal except for the cyanosis. Roentgenographic examinations showed a small amount of gas in the intestinal tract, but the usual bubble in the stomach was absent.

The child then began to vomit pink material and passed a uniformly hemorrhagic, red stool. Cyanosis became extreme, and the abdominal distention increased, but the temperature remained normal, although respiration was shallow. An enema failed to relieve the distention, and supportive therapy, including oxygen, was of no assistance. The continual vomiting, bloody stools, tense abdomen and shock pointed to intra-abdominal disease, but a precise diagnosis could not be established, and surgical therapy was deemed inadvisable. The baby died seventy-one hours after birth.

Diagnosis from clinical observations was questionable intussusception, volvulus or tracheoesophageal fistula. Anatomic diagnosis was absence of transverse aortic arch, patent ductus arteriosus, defects of interauricular and interventricular

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5. Hamburger, L. P.: Congenital Cardiac Malformation with Complete Interruption of Isthmus Aortae and Transposition of Great Arteries, Bull. Johns Hopkins Hosp. **61**:421-428 (Dec.) 1937.

6. Evans, W.: Congenital Stenosis (Coarctation), Atresia, and Interruption of Aortic Arch: Study of Twenty-Eight Cases, Quart. J. Med. **2**:1-31 (Jan.) 1933.

septums, hypoplasia of aortic valve, cardiac dilatation (right side), acute passive congestion of viscera and hemorrhage into alimentary tract.

Observations at Autopsy.—The autopsy was performed one-half hour after death, and much of the blood in the vessels had not yet clotted. Accordingly, the greatly swollen and congested liver, as well as the extremely dilated right auricle and ventricle, discharged a large amount of blood and collapsed to normal proportions when the mammary veins were sectioned. At the same time most of the cyanotic mottling of the upper part of the body disappeared. The subcutaneous tissues were somewhat edematous, but the body cavities contained no excess of free fluid. The viscera exhibited a striking degree of congestion; the lungs were somewhat less congested than the other organs, but small patches of atelectasis and of early pneumonia were present.

The more significant observations were of the heart and great vessels (fig. 1) and the alimentary tract. The heart was greatly dilated, the enlargement being entirely right sided. A large foramen ovale, 2.4 cm. in diameter, with but a narrow rim of membranous flap along one edge, allowed free communication between

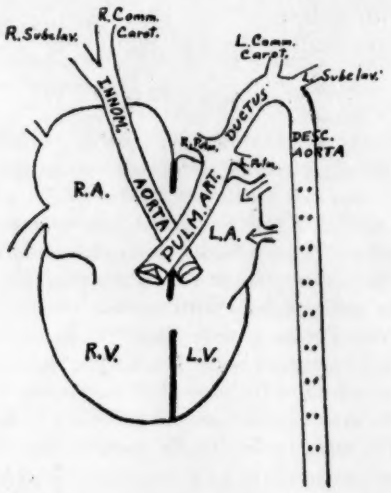

Fig. 1.—Diagram of heart and great vessels of 3 day old infant, showing absence of transverse aortic arch, the descending aorta arising from the portion of the trunk which includes the pulmonary artery, ductus arteriosus and aorta, patent interauricular and interventricular septums, hypoplasia of aortic valve and dilatation of right side of heart.

the two atria. A second defect, 6 mm. in diameter, occupied the upper portion of the interventricular septum. The tricuspid, pulmonary and mitral valves were normal.

The aortic valve was poorly developed and consisted of a large irregular cusp and a second rudimentary one; a coronary ostium lay behind each cusp. The ascending aorta was thin walled and but little smaller than normal. It ended on the right side of the midline as the innominate artery, which divided in the usual manner into the right common carotid and subclavian arteries. No channel or fibrous cord could be demonstrated at the level where the transverse portion of the aortic arch normally lies.

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The pulmonary artery arose in the usual fashion, but it was large in its first portion, having a circumference of 3 cm. The left and right pulmonary arteries arose normally and had the usual distribution. Just beyond their orifices a channel, 1.2 cm. in circumference, represented the widely patent ductus arteriosus; it had a somewhat thickened, slightly wrinkled wall. This channel continued directly into the descending portion of the aortic arch and the thoracic aorta. The left common carotid and left subclavian arteries took origin from the descending arch just beyond the segment that represented the ductus. The remainder of the aorta and its branches were normal.

The alimentary tract was remarkable in that it was the site of intense, diffuse congestion, with hemorrhage into the mucosa of much of the small intestine. Histologic study revealed small tags of fibrinous and fibrinopurulent exudate attached

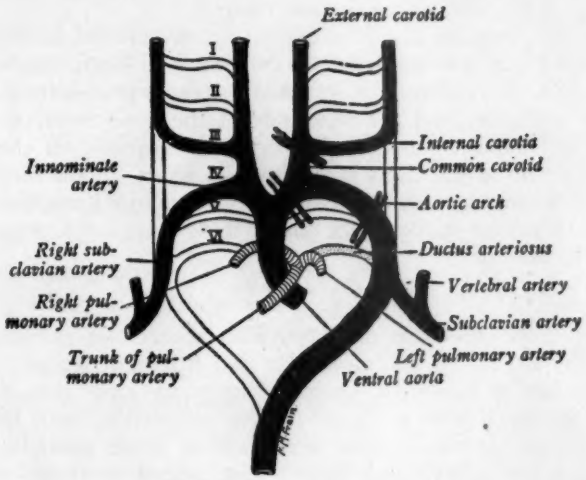

Fig. 2.—Diagram showing the aortic arches and their derivatives in human embryos (from Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text Book of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1920, p. 263). The vessels indicated in black normally persist into postnatal life, but in this case the Y-shaped segment between double lines, including the fourth left aortic arch disappeared, while the ductus arteriosus and part of the dorsal aortic root between the left third and fourth aortic arches persisted.

loosely to minute superficial defects in the mucosa over some of these foci of hemorrhage. Hemorrhagic fluid was observed in both the small and the large intestine. No point of intussusception or other obstruction was present, and the mesenteric vessels were normal except for venous congestion. The esophagus and stomach were normal.

COMMENT

The mechanism of absence of the transverse portion of the aortic arch lies in atrophy or aplasia of the fourth left vascular arch that normally becomes the definitive aortic arch (fig. 2).[7] The proximal portion of each sixth arch normally becomes one of the main pulmonary arteries; the distal portion of each disappears after the ductus arteriosus, which

7. Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text Book of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1920, p. 263.

represents the distal portion of the left sixth arch, is no longer needed. With atrophy of the anlage of the aortic arch, the ductus persists and continues into the descending aorta as in fetal life.

The segment of the dorsal aortic root lying between the left third and fourth aortic arches which usually disappears evidently remained open in this instance, which accounts for the rather remarkable origin of the left common carotid artery from the portion of the trunk which included the pulmonary artery, ductus arteriosus and aorta.

The right side of the heart became progressively overloaded from receiving blood from the left auricle and ventricle via the two septal defects. The rising venous pressure was reflected in visceral congestion, and, when this became severe enough in the liver, it was transmitted beyond to the portal bed and led to congestion of the intestine with hemorrhage. Symptoms of intra-abdominal disease ensued.

Most of the body received inadequately oxygenated blood from the right ventricle, which mixed with blood that had been returned to the right side of the heart from the left side via the septal defects. Only the right upper extremity and the right side of the head received fully oxygenated blood. Theoretically, earlier onset of cyanosis on the left side, with enlargement of the right border of the heart, might have led to a presumptive diagnosis of the cardiac and vascular malformations, but no such observation was made, since the striking symptoms pointed rather to abdominal disease.

SUMMARY

An example of the rare malformation, absence of transverse aortic arch, with defects of the interauricular and interventricular septums, in a newborn infant is presented. Overloading of the right side of the heart led to an extreme degree of acute passive congestion, with hemorrhage into the intestine. The symptoms were those of acute abdominal disease.

The literature is reviewed, and 1 case added to those of Abbott's group *b* of high absence of aortic arch, which makes a total of 13 possible cases so far reported in this category.

White Plains Hospital Association.

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ASEPTIC MENINGITIS FOLLOWING IMMUNIZATION WITH DIPHTHERIA TOXOID

HYMAN B. STILLERMAN, M.D.
ATLANTA, GA.

THE OCCURRENCE of a neurologic complication during the course of immunization against diphtheria with toxoid is most unusual. A review of the literature revealed a report by Schioppa[1] of a case of transitory paralysis of the palate following immunization with diphtheria toxoid. The present case is 1 in which aseptic meningitis occurred during immunization with diphtheria toxoid.

REPORT OF A CASE

B. A. was an 18 year old white nurse in training at another hospital. Her reaction to the Schick test was found to be positive; consequently, she was started on a course of immunization with diphtheria toxoid. Because of a strong reaction to the Moloney test, the course of immunization was begun cautiously. On Sept. 19, 1946, she received 0.05 cc. of toxoid, the inoculation being followed by a severe local reaction. Therefore, the second dose, seven days later, was not increased, and this time she had only a slight reaction following the injection. The third dose, 0.10 cc., was administered eight days later, on October 4. That night, the patient's left shoulder became red and sore at the site of inoculation. The following day, these symptoms were intensified but did not incapacitate her. A dull frontal headache developed forty-eight hours after the last inoculation, and this increased in intensity as the day progressed. Seventy-two hours after her inoculation, the headache had become increasingly severe, and nausea and vomiting developed. On October 8, four days after her last inoculation, the patient was admitted to Grady Hospital with complaints of severe photophobia which appeared that morning and an excruciating headache which was made worse by moving her eyes. The headache had spread backward to cover her entire head, and she described it as feeling like "someone hammering on my head." She also felt warm on the day of admission but did not have a chill. There was no stiffness of the neck, vertigo, deafness, or infection of the upper respiratory tract. The patient had been in good health and had never had headaches. There was no allergic history. Her mother had migraine headaches.

From the Medical Service, Grady Hospital, and the Department of Medicine, Emory University School of Medicine.

1. Schioppa, L.: Transitory Paralysis of Palate Following Diphtheric Immunization with Anatoxin, Prat. pediat. **12**:531, 1934.

On examination, her temperature was 100 F.; pulse rate was 96 and respiratory rate 18. Blood pressure was 110 systolic and 70 diastolic. The sites of inoculation of the toxoid were red and indurated. The patient would not move her eyes voluntarily. There was no nystagmus; the extraocular movements were intact; the pupils and the fundi were normal. Otoscopic examination and rough auditory tests gave normal results. The neck was stiff. Neurologic examination revealed a questionable Kernig reflex bilaterally, no muscular weakness and intact sensory pathways and physiologic reflexes.

Laboratory Data.—The hemoglobin concentration was 14.8 Gm.; the leukocyte count was 13,400, with 71 per cent polymorphonuclear cells, 26 per cent lymphocytes and 3 per cent monocytes. The erythrocyte sedimentation rate was 80 mm. per hour. Routine urinalysis gave normal results. The spinal fluid pressure was slightly increased to 190 mm. of water; the dynamics were free. The fluid was clear and colorless, but it contained 110 cells, 60 per cent of which were polymorphonuclear cells; protein measured 43 mg. and sugar 80 mg., per hundred cubic centimeters. No bacteria were demonstrated on smear.

The patient was treated symptomatically and gradually improved on this regimen. Her temperature became normal in twenty-four hours and remained so for the duration of her stay in the hospital. Stiffness of the neck gradually disappeared during the next three days, and the soreness of her ocular muscles lessened and disappeared after five days. Her photophobia was completely gone in three days. She was able to get up on the fifth day and noted that a dull frontal headache would develop about ten minutes after she arose. This headache was different from the one that brought her to the hospital and would disappear promptly on lying down in bed. However, she continued to get up, and, on the day of discharge, the headache would appear after she was up one to one and one half hours.

Lumbar puncture was repeated on the fourth day in the hospital, and the only abnormal observation was the presence of 120 cells, 95 per cent of which were lymphocytes. Another lumbar puncture performed four days later revealed 35 cells (all lymphocytes).

The patient was discharged from the hospital on the eighth day and sent home for convalescence. Four days after she left the hospital, her headaches completely disappeared. She then carried on all her normal activities. She returned in two weeks for reexamination. A lumbar puncture done at that time showed 15 lymphocytes. Acute and convalescent serums studied for the presence of antibodies of the virus encephalitides, namely, St. Louis type (acute epidemic encephalitis), encephalitis (Japanese) B and eastern and western equine encephalomyelitis, as well as mumps encephalitis, were negative. She had no complaints and showed no residual effects from her illness.

COMMENT

While it is true that reports in the literature on neurologic complications following inoculation with diphtheria toxoid are sparse, such is

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not the case with other immunizing agents. Robinson[2] reviewed the literature with reference to these complications and stated, "Among the offenders are every type of serum and vaccine." He specifically incriminated rabies, smallpox and typhoid vaccines, scarlet fever toxin, diphtheria and scarlet fever antitoxins and antipneumococcic and antimeningococcic horse serums. These agents have given rise to two types of neurologic complications, namely, peripheral and central nervous system manifestations. Manifestations of the latter type have often resulted in spinal fluid showing increase in pressure, number of cells and amount of protein. The mechanism of the neurologic manifestations and complications following inoculation with vaccines and serums has never been determined, although several theoretic explanations have been advanced.

The symptoms reported in cases of severe generalized constitutional reactions following inoculation with diphtheria toxoid and those in the present case are similar except for the severe photophobia in our case. It is possible that other cases of aseptic meningitis may have been overlooked because of omission of examination of spinal fluid.

36 Butler Street, S. E. (3).

2. Robinson, L. J.: Neurologic Complications Following the Administration of Vaccines and Serums, New England J. Med. **216**:831, 1937.

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Abstracts from Current Literature

Biochemistry, Bacteriology, and Pathology

SULFONAMIDE SENSITIVITY DETERMINATIONS OF HEMOLYTIC STREPTOCOCCI ISOLATED FROM PATIENTS BEFORE AND AFTER TREATMENT WITH SULFADIAZINE. THOMAS L. HARTMAN, Bull. Johns Hopkins Hosp. **79**:342 (Nov.) 1946.

From 40 patients streptococci of the same type were removed in both the acute and the convalescent phases of streptococcic infections. None of the hemolytic streptococci isolated after administration of a course of sulfadiazine therapy showed any evidence of the development of resistance to sulfadiazine.

LYTTLE, Los Angeles.

REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM: III. EFFECTS OF VARYING AMOUNTS OF PNEUMOCOCCAL POLYSACCHARIDE ON REVERSED PASSIVE ANAPHYLAXIS IN GUINEA PIGS; IV. A SIMPLE ROUGHLY QUANTITATIVE METHOD OF MEASURING CIRCULATING POLYSACCHARIDE. H. ROWLAND PEARSALL, STANTON L. EVERSOLE and OSCAR SWINEFORD JR., J. Allergy **17**:190 (July) 1946.

A method for measuring a circulating polysaccharide is described.

Reversed passive anaphylaxis is produced in guinea pigs by injecting an excess of pneumococcus polysaccharide an hour before injecting type-specific antipneumococcus serum.

HOYER, Cincinnati.

A STUDY ON THE MECHANISM OF ACTION OF PENICILLIN AS SHOWN BY ITS EFFECT ON BACTERIAL MORPHOLOGY. A. MURRAY FISHER, J. Bact. **52**:539 (Nov.) 1946.

The exact mechanism by which penicillin exerts its antibacterial effect is not clear. The author tries to throw some light on this fundamental problem by considering alterations which penicillin produces in the morphology of susceptible bacteria. In vitro, penicillin causes an enlargement of staphylococci, followed by lysis. This is apparently due to interference with their normal stimulus to division and multiplication, rather than to complete inhibition of growth. Penicillin produces the same effect, to a lesser degree, on beta (hemolytic) streptococci and pneumococci. In the case of the latter the capsule remains intact for some time after the cell body is destroyed, and this effect is apparently a biologic, rather than a physical or chemical, reaction, since it occurs only under conditions in which the organism is capable of growth. The clinical significance of these findings is discussed, and reference to the original paper is recommended.

STOESSER, Minneapolis.

Metabolism; Infant Feeding; Milk and Other Foods

THE DISTRIBUTION OF WATER AND FAT IN THE SKIN AND MUSCLE OF THE DOG DURING CHRONIC AND ACUTE DEHYDRATION. BENJAMIN DE BOER, Am. J. Physiol. **147**:49 (Sept.) 1946.

The author carried out many experiments with dogs in order to reveal the variation in both fat and water content of the tissues and organs when chronic

dehydration was produced by withholding food and water. He found that a degree in fat of 4 per cent in skin and of less than 0.5 per cent in skeletal muscle occurred. Data on water content of normal and of dehydrated tissues were more consistent and significant when calculations were based on fat-free samples. Normal skin and muscle then differed less than 5 per cent in water content. The percentage loss of water during dehydration was greater for skin than for muscle. High fat content was correlated with a lower percentage of water in the fat-free constituents of the skin of normal dogs. During chronic dehydration, the loss of water by skin was less for obese dogs than for lean dogs.

STOESSER, Minneapolis.

CREATINE EXCRETION IN ADOLESCENTS. N. W. SHOCK, Child Development **16**: 167 (Sept.) 1945.

Measurements of creatine and creatinine were made on morning urine specimens from 30 girls and 40 boys. Specimens of urine were collected on each of two successive mornings at six month intervals in the same children between the ages of 13.0 and 17.5 years. The ratio of creatine to creatinine content of the same urine sample was calculated and used in the analysis of the data. Results showed a maximum in the average output of creatine in both boys and girls at the age of 14.5 years, which in the boys was associated with maximum growth rate in stem length. In both boys and girls maximum creatine to creatinine ratios were found associated with periods of maximum increase in muscular strength. No correlation between creatine to creatinine ratio and basal metabolism could be demonstrated. In late-maturing girls, there was an increase in the creatine to creatinine ratio either before or at menarche, followed by a rapid fall thereafter. In both boys and girls, children who matured early showed lower creatine to creatinine ratios at a given chronologic age than those who matured late.

THE ACTIVITY OF PENICILLIN IN RELATION TO BACTERIAL SPORES AND THE PRESERVATION OF MILK. HAROLD R. CURRAN and FRED R. EVANS, J. Bact. **52**:89 (July) 1946.

The authors made a study of the preserving action of penicillin in milk containing viable bacterial spores. Bacillus cereus, Bacillus mycoides, Bacillus albolactis and Bacillus metiens were relatively resistant. Thirteen other species were relatively susceptible to penicillin, as was manifested by strong sporicidal or prolonged sporistatic activity in a drug concentration of 5 units per cubic centimeter. This concentration sterilized many of these cultures.

Clostridium botulinum was able to produce spoilage in the presence of 5 units per cubic centimeter of penicillin. However, the process was delayed by the drug. It appears, therefore, that penicillin has no application in the preservation of food. In combination with mild heating, it might have utility as a preservative or spoilage-delaying agent in certain nonfood materials.

STOESSER, Minneapolis.

DEPRESSION OF GAMMA GLOBULIN IN HYPOPROTEINEMIA DUE TO MALNUTRITION. EDWIN G. KREBS, J. Lab. & Clin. Med. **31**:85 (Jan.) 1946.

A case of uncomplicated nutritional hypoproteinemia in a girl 15 years of age is reported. Electrophoretic determinations of the plasma proteins were made before and after a period of high protein intake. A very low level of gamma globulin in the plasma was recorded before the hypoproteinemia was corrected. The agglutination reaction of the patient's serum with typhoid H antigen vaccine

was negative five weeks after the completion of immunization with typhoid antigen. The possible significance of the reported observations in regard to antibody production and resistance to infection in states of malnutrition is pointed out.

WILKINSON, Galveston, Texas.

SOME ASPECTS OF PROTEIN METABOLISM IN INFANTS AND CHILDREN. F. W. CLEMENTS, M. J. Australia **2**:404 (Sept. 21) 1946.

Clements discusses the application of the various theories of protein metabolism to the methods of infant feeding and reports the results of a study of the effects of diets rich in protein, given in certain special circumstances, on the growth of infants and young children. It is pointed out that experimental work indicates that in the process of resynthesis of proteins from the metabolic pool, certain proteins seem to have a higher priority than others. Thus, the protein fraction of hemoglobin appears to have first claim on these protein components, while plasma proteins and those of the liver and visceral musculature have a higher priority than those of skeletal muscles and skin. Consequently, during periods of absolute or relative protein starvation in infancy, one of the first structures to show the effects of protein privation is skeletal muscle, which loses tone and volume.

Young infants do not tolerate starvation or even semistarvation well, even when presumably sufficient fluid is given. They quickly take on a characteristic appearance, becoming obviously thinner, while the face is drawn and bluish. The skeletal muscles become soft and flabby. In such cases, additional protein is indicated in the period of convalescence, and for this purpose Clements used the following prescription with spectacular success in the restoration of body weight and muscle tone: equal parts of fine casein (90 mesh) and dried skimmed milk. This mixture is made into a fairly thick gruel in water and given with each normal feeding, starting with ½ teaspoonful (about 2.5 cc.) and increasing rapidly to 1½ to 2 medicinal teaspoonfuls (8 to 10 cc.) five times daily. The use of rich protein supplement is indicated for young infants who have lost weight through semistarvation, whether due to illness or to an incorrect feeding routine. The additional protein leads to a more rapid recovery of normal weight than is usually achieved by the use of breast milk alone or the usual cow's milk formulas.

It is after he has graduated to three meals a day that the normal healthy infant is likely to become the victim of an inadequate protein intake. Three meals a day can furnish satiety and sufficient calories and vitamins and yet be lacking in protein, particularly when milk and meat are poorly taken. Infants in the second year probably need 3.5 to 4 Gm. of protein per kilogram per day. Insufficient protein intake in older infants (10 to 24 months of age) results in stationary weight, capricious appetite, reduction in hemoglobin concentration and poor skeletal muscle tone. In treatment in such cases, Clements used a concentrated form of protein, consisting of 60 per cent commercial casein, 20 per cent dried skimmed milk, 10 per cent wheat germ (powdered) and 10 per cent maize protein. Starting with 1 teaspoonful (5 cc.) in 2 ounces (60 cc.) of milk cooked for one minute, with a pinch of salt and a little sugar, this mixture is worked up to 4 to 6 tablespoonfuls (60 to 90 cc.) a day. Twenty of 25 patients so treated showed a similar response, characterized by the following improvements: (*a*) large weekly gains in weight, evident in some after one week's treatment, but more frequently commencing in the second or third week; (*b*) recognizable improvement in muscle tone after a few weeks on the diet; and (*c*) the frequent observation by the mother that the child's appetite, particularly for milk, had greatly improved.

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Once appetite was restored and the child had been established on a diet containing at least 40 Gm. of protein a day, the protein powder was discontinued and the good progress was maintained.

GONCE, Madison, Wis.

ADDITION OF BEEF FLAKES TO THE DIET OF NURSLINGS. A ROSSIER and J. MATET, Arch franç. de pédiat. **3**:151, 1946.

Meat is not usually considered a proper item in the nutrition of infants less than 1 year old. The eruption of the canine teeth at the age of 14 or 15 months signalizes the period when meat may be digested. Leading French pediatricians recommend beef soup at the twelfth month and offer 15 to 20 Gm. of finely minced beef pulp at 15 months. Certain authors, however, advise the use of this item much earlier and even offer to the infant dishes of liver, brains and kidneys. The difficulty of preparing such complicated recipes and, more important, their excessive quantities of purine bodies and cholesterol caused these suggestions to be given only passing favor.

In its wealth of amino acids and its high content of iron, iodine and vitamins, beef represents, theoretically at least, a food of great interest. The problem of serving it, however, in a form readily digested and easily assimilated has proved to be almost insolvable.

Rossier and Matet conceived the idea of developing a meat flour with a process imitating that of Tobler whose dehydrated vegetables were readily adapted to the digestive capacity of nurslings. After many trials, they succeeded in manufacturing a product consisting of beef flakes intimately mixed with an excipient rich in glucosides, such as cereals, vegetables or mixtures of the latter foodstuffs.

To these preparations were added in proper amounts the essential minerals sodium, phosphorus and calcium. In its final form the food resembled powdered milk and could be used in simple dilution without cooking.

Experimentation with young white rats, continuing for two months and checked by controls fed on casein and lactalbumin, showed satisfactory growth. A number of infants between 5 and 10 months of age were then subjected to substitution of the usual milk ration with the meat powder. There were no digestive disturbances, and the stools showed total absence of muscle fibers. Average gain in weight was maintained. The authors recommended the preparation for use in places where the milk supply is restricted.

AMESSE, Denver.

FURTHER STUDIES ON HUMAN LACTATION. J. VAN ESPEN, Arch. franç. de pédiat. **3**:193, 1946.

While knowledge of cow's milk is extensive, there are many problems concerned with mother's milk which need clarification, especially in the management of so-called lactariums, established throughout Western Europe during the past three decades.

Van Espen begins a series of inquiries into the physiology of lactation. In his valuable monograph he considers the following problems: (1) early criteria for the abundant supply of milk in a given person, (2) correlation between the fat content and other essential elements, (3) relation of the fat index to the health of the nursling, (4) evolution of the fat index as lactation proceeds and (5) influence of diet on the volume and the permanency of milk secretion.

AMESSE, Denver.

SEVERE MALNUTRITION; ATHREPSIA, AND THE ATHREPTIC "TERRAIN." G. MOURIQUAND, Presse méd. **53**:441 (Aug. 18) 1945.

So many factors enter into the development of the athreptic state that is is difficult to isolate the fundamental terrain on which the condition develops. Experimentally, it has been shown that lack of vitamin C or of protein will produce an irreversible condition in the cells of the body, and failure to assimilate nourishment leads shortly to death. The classic picture of athrepsia in babies is seen in persons returning from prison or concentration camps. General malnutrition reduces the natural immunity, and this condition is soon complicated with infection, but the immunity produced by diphtheria toxoid is not affected. Pigeons reduced to an athreptic state lose their vestibular equilibrium. Even though the deficiency has been carried to the irreversible stage, this function of the nervous system can be reestablished.

Mouriquand points out that this irreversible stage cannot be diagnosed clinically and that surprising recoveries may occur in seemingly hopeless cases.

DAFFINEE, Melrose, Mass.

CALCIUM AND PHOSPHORUS DEFICIENCY OF FIVE YEARS' DURATION. H. HINGLAIS and M. HINGLAIS, Presse méd. **53**:595 (Nov. 3) 1945.

In France there has been a tremendous increase in the number of spontaneous fractures due to osteoporosis. The average French diet has contained less than 50 international units of vitamin D for all ages, and the calcium deficit has been from 50 to 92 per cent for the population over 6 years of age. Infants and children have received 90 per cent or more of their calcium requirements.

The authors urge immediate restoration of the milk stores by the building up of dairy production and the importation of milk and cheese. Calcium carbonate should be added to bread and vitamin D incorporated into butter or sugar.

DAFFINEE, Melrose, Mass.

NEUROPHYLACTIC ACTION OF BREAST MILK. J. LEVESQUE and R. BASTIN, Presse méd. **54**:251 (April 20) 1946.

The authors advance the thesis of a specific action of breast milk in combating toxic and infectious conditions of the newborn infant and in preventing pylorospasm and pyloric stenosis. The amount of breast milk necessary to achieve results is much less than that which is necessary to supply sufficient calories, protein, fat and sugar. Sixty grams a day may be enough. The essential element of the action of such small quantities consists in the protection of the immature nervous system. The protective substances remain unidentified, but they seem to be thermostabile.

DAFFINEE, Melrose, Mass.

DEHYDRATION BY DEPRIVATION OF FLUIDS. E. KERPEL-FRONIUS, Paediat. danub. **1**:33 (Jan.) 1947.

Thirst causes a special type of dehydration. Analyses of brain and muscle tissues indicate, as shown by earlier balance experiments, that the loss of fluid is divided between the extracellular and the intracellular parts of the body. In consequence of this division of the total loss of body water between the two fluid components, plasma volume is conserved even in cases of extreme total water losses (up to 30 per cent of body weight). The loss of extracellular water is proportionately greater than the loss of body chloride. In this type of dehydration no parallelism is observed between salt and water. Hyperchloremia and hypernatremia are coexistent with excessive chloropenia.

FROM THE AUTHOR'S SUMMARY.

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Vitamins; Avitaminoses

THE CHEMICAL CYTOLOGY OF THE RAT'S ADRENAL CORTEX IN PANTOTHENIC ACID DEFICIENCY. HELEN WENDLER DEANE and JOHN M. MCKIBBON, Endocrinology **38**:385 (June) 1946.

Weanling male rats placed on a purified diet deficient in pantothenic acid grew poorly in comparison with their controls and presented other symptoms commonly described for this deficiency. Moreover, their adrenal cortices became relatively large, while the zonae reticularis and fasciculi were progressively drained of ketosteroids and gave cytologic evidence of exhaustion. Signs of degeneration were noted in kidneys, liver and thymus, suggesting that a pantothenic acid deficiency acts as an "alarming agent" for the rat. Such agents cause the release of pituitary adrenotropin which stimulates the adrenal gland to enlarge and to increase its secretion of corticosterone. A deficiency of pantothenic acid is so severe an "alarming agent" that the adrenal gland becomes exhausted of corticosterone.

JACOBSEN, Buffalo.

TREATMENT OF INFANTILE PELLAGRA, ASSESSMENT OF THE VALUE OF PROTEIN HYDROLYSATES. T. GILLMAN and J. GILLMAN, Lancet **2**:446 (Sept. 28) 1946.

The authors observed a series of South African native children suffering from a syndrome of malnutrition which consisted of "characteristic dermatosis" with varying degrees of edema, hypoproteinemia, steatorrhea and diarrhea. The mortality was high and was related to the degree of fatty changes in the liver. Several groups were tried on different treatments: (1) normal diet, (2) normal diet and supplementary vitamins, (3) parenteral administration of liver extract, (4) oral administration of liver extract and vitamins and (5) (*a*) use of protein hydrolysate, (*b*) powdered stomach U.S.P. ("ventriculin") and (c) powdered stomach and vitamins. Comparability of groups was sought by assigning the children according to the degree of fatty change in the liver, as observed in biopsies. The case fatality rates were recorded for each diet.

Treatment with powdered stomach U.S.P. alone gave the best results, with a fatality rate of 6 per cent in 50 cases. Rates for the other forms of therapy varied from 30 to 73 per cent. The authors were particularly opposed to treatment with protein hydrolysate (60 per cent mortality in 20 cases). They believe that in severe malnutrition a homeostasis is set up with peculiar regulatory mechanism and that if these mechanisms are tampered with, as by the administration of an excess of a vitamin or other substance, the results are poor.

It is noted that, although the evidence for the beneficial effect of "ventriculin" appears to be good, the condemnation of protein hydrolysates is on less secure ground. Three hydrolysates were used, and the number of patients treated with each was very small. No mention is made of age-specific fatility rates or other possible factors influencing mortality.

HODGES, Cleveland.

VARIATIONS IN VITAMIN C. P. ROHMER, N. BESSONOW, R. SACREZ and H. LEROUX, Arch. franç. de pédiat. **3**:220, 1946.

It has been demonstrated that the rapid loss of vitamin C in the course of infectious diseases of childhood produces a latent scurvey. This is especially evident in cases of whooping cough. The authors have interested themselves in the

cause and the significance of accelerated loss of ascorbic acid and its derivatives. The normal content of these substances was first determined in an elaborate study of Bessonow. The level was found to be reduced in patients with tuberculosis, meningitis, bronchopneumonia and various other acute infections. A second series of investigations were made to determine whether the therapeutic administration of ascorbic acid, using a dose of 5 to 50 mg. per killogram, would prevent the development of subclinical scurvey in the course of a given infection.

All analyses of the ascorbic acid level were made on the cerebrospinal fluid, and these were checked by coincident estimations of that substance in the urine. The report provides detailed experiences with 12 patients with infections and concludes with the recommendation that massive amounts of vitamin C preparations be offered in the management of infectious diseases of childhood.

AMESSE, Denver.

IN VITRO EFFECT OF VITAMIN D_2 AND DIHYDROTACHYSTEROL ON INORGANIC PHOSPHORUS OF SERUM. C. DETONI, Riv. di clin. pediat. **40**:656 (Nov.) 1942.

Neither a relatively pure type of irradiated ergosterol ("vigantolo") nor dihydrotachysterol caused lysis of the organic phosphorus compounds of blood serum to increase the inorganic phosphorus compounds in experiments in vitro. The earlier positive results of Frontali and De Toni were perhaps due to the action of isomers in the ergosterol used at that time.

HIGGINS, Boston.

Hygiene; Growth and Nutrition; Public Health

PHYSICAL GROWTH FROM BIRTH TO TWO YEARS: II. HEAD CIRCUMFERENCE, PART I. A REVIEW AND SYNTHESIS OF NORTH AMERICAN RESEARCH ON GROUPS OF INFANTS. HOWARD V. MEREDITH, Child Development **17**:1 (March-June) 1946.

This paper constitutes part I of a two part study dealing with head circumference during the first two years of postnatal life. It presents a review and synthesis of North American research to date on groups of infants. Its companion paper will colligate the studies made in North America pertaining to the growth of individual persons. Source materials are drawn from 35 investigations—29 published over the years 1853 to 1945 and 6 not previously reported in published form. These materials are integrated with reference to the information they afford on 10 problems. That is, intercomparisons are made and generalizations derived on head girth in relation to age, sex, lineage, socioeconomic status, secular period, diet, disease, prematurity, birth molding and birth order.

FROM THE AUTHOR'S SUMMARY.

THE WELL CHILD. D. W. VAN GELDER, New Orleans M. & S. J. **99**:277 (Dec.) 1946.

An annual visit to a physician is urged. This visit should include, in addition to a complete physical examination, a comprehensive review of the past history and a frank discussion of the child's physical and mental problems. If appropriate, laboratory work should be done. Immunization procedures should be reviewed and brought up to date, if necessary. It is the physician's duty to help each child to make proper adjustments as naturally as possible. The child and the parents should be privileged to enjoy the counsel of the physician in both physical and mental health problems.

BERKLEY, Beverly Hills, Calif.

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Newborn

EVIDENCE OF MATERNAL RH SENSITIZATION WITHOUT EVIDENCE OF HEMOLYTIC DISEASE IN THE NEWBORN. DONALD H. KARIHER and DOROTHY I. MILLER, Am. J. M. Sc. **212**:327 (Sept.) 1946.

The authors describe 2 cases of mothers, gravida II and gravida III, who were Rh negative and whose serum contained Rh antibodies, to whom apparently normal, Rh-positive infants were born. The authors discuss two possibilities to explain these unusual cases.

HENSKE, Omaha.

INFECTIOUS DIARRHEA OF THE NEWBORN. HENRIETTA HERBOLSHEIMER, Illinois M. J. **90**:6-9 (July) 1946.

Four sizable epidemics of infectious diarrhea of the newborn occurred in Illinois hospitals during the first five months of 1946. Owing to the inaccuracy of reporting, one cannot form a reliable impression of the incidence of the disease. From 1941 to June 1946, inclusive, fourteen epidemics were reported in Illinois. There were probably additional unrecorded outbreaks. Forty-seven deaths attributable to infectious diarrhea of the newborn were reported during the first five months of 1946. There is no way of knowing the exact number of cases of diarrhea.

The author reviews the literature on infectious diarrhea of the newborn. She includes discussions of the symptoms, differential diagnosis, complications, prognosis, treatment, factors contributing to origin and spread and the prevention and control.

The author points out that the lack of a uniform definition of diarrhea and the fear of stigma on the part of physicians and institutions have probably contributed to the paucity of reports of cases received in health departments. The Illinois Department of Public Health offers aid to the institutions in establishing good facilities and technics for prevention of epidemic diarrhea. The Department of Public Health, through the Division of Laboratories has the scientific means to carry on complete bacteriologic and virologic study of the individual cases.

Prompt reporting may be anticipated to start a chain of reactions, including the adoption of isolation nursing technics, immediate application of therapeutic measures and the instigation of scientific study of this ever present threat to the practice of neonatal pediatrics in institutions.

BARBOUR, Peoria, Ill.

THE EFFECT OF THE PREDIABETIC STATE ON THE SURVIVAL OF THE FETUS AND THE BIRTH WEIGHT OF THE NEWBORN INFANT. HERBERT C. MILLER, New England J. Med. **233**:376 (Sept. 27) 1945.

One of the outstanding characteristics of infants born to diabetic mothers is a high fetal and neonatal mortality rate. In addition, there occur in some infants born to diabetic mothers striking somatic and visceral changes, among which are an increased birth weight, cardiomegaly, hyperplasia of the islands of Langerhans, excessive extramedullary erythropoiesis, hyperplasia of the adrenal glands and an increase in the eosinophilic elements of the anterior pituitary body. The mortality rate of 8.3 per cent for the prediabetic group is significantly higher than that of 2 per cent for the nondiabetic group.

It is a generally recognized fact that the mortality of newborn infants increases with the age of the mothers. The mortality ranges from 3 per cent for

mothers between 16 and 20 years of age; 5.5 per cent for those between 20 and 30 years; 10.3 per cent for those between 30 and 40 years; to 100 per cent for those between 40 and 45 years.

GENGENBACH, Denver.

THE RH FACTOR AND ERYTHROBLASTOSIS. J. F. HOET, P. DE SOMER and J. VANDENBROUCKE, Presse méd. **54**:249 (April 20) 1946.

The authors present a series of investigations which confirm previous studies of the Rh factor. Data on 60 families in which an erythroblastic baby had been born were as follows: In 53 families the father was Rh positive, the mother Rh negative and the baby Rh positive. In 2 families the mother was Rh negative, and her serum contained anti-Rh agglutinins. The father's blood was not obtained. In 3 families both father and mother were Rh negative and no anti-Rh agglutinins were found in the serum of these mothers at ten days, seven weeks and seven weeks respectively. In 2 families both father and mother were Rh positive. In 1 of these, in which a baby who died of erythroblastosis was produced, anti-Rh_2 agglutinins were found in the mother's serum six months after delivery.

DAFFINEE, Melrose, Mass.

KERNICTERUS IN THE NEWBORN AND ITS OUTCOME. R. GIUNTINI, Riv. di clin. pediat. **40**:513 (Sept.) 1942.

Seven cases of kernicterus are reported. The clinical aspects, the pathogenesis and the treatment of the residual nervous symptoms are discussed.

HIGGINS, Boston.

PREVENTION OF PHYSIOLOGIC LOSS OF WEIGHT IN THE NEWBORN. A. INGIULLA, Riv. di clin. pediat. **40**:590 (Oct.) 1942.

Seventeen methods of modifying the initial loss of weight in newborn infants are recorded. While this loss of weight is usual, it is not necessarily present and can easily be influenced and modified.

HIGGINS, Boston.

ERYTHROBLASTOSIS FETALIS IN THE FETUS AND IN THE NEWBORN INFANT. A. CASAUBON, S. CASSAY and I. DÍAZ, Arch. argent. de pediat. **26**:107 (Aug.) 1946.

Three cases of erythroblastosis fetalis with different clinical manifestations are presented. The first case presented the clinical picture of obstructive jaundice and the other 2 cases the picture of anemia. In 2 cases the mother was Rh negative, and the father and baby were Rh positive. In the third case the parents were Rh positive but genetically different: the mother was subtype Rh′ and the father subtype Rh_0'

All the patients were successfully treated with transfusions of type O, Rh-negative blood.

ROJAS, Boston.

EVOLUTION AND TREATMENT OF ERYTHROBLASTOSIS FETALIS. J. J. MURTAGH, Arch. argent. de pediat. **26**:116 (Aug.) 1946.

All the cases of erythroblastosis fetalis with live fetus from the Instituto de Maternidad de la Sociedad de Beneficencia, in addition to those of 2 private patients, are studied. All the patients (13) presented early jaundice and anemia of variable degree. Four of these babies died: 1 of them shortly after birth, 1 on the fourth day, 1 on the fifth day and 1 at the age of 2 months. One of the 9

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infants who survived presented the Cecile Vogt syndrome; the remaining 8 developed well and were followed for from several months to three years (the last infant, born in 1943, was treated for icterus gravis, but later serologic studies revealed the erythroblastosis).

Seven of the 9 survivors were breast fed by the mother for several months. The author insists on the advantage of not depriving these babies of the maternal feeding, though, he states, the condition of the blood should be watched.

Transfusions of Rh-negative, compatible blood, without agglutinins, must be early and abundant, until a volume equivalent, or almost equivalent, to the blood volume of the body has been introduced.

In cases of polycythemia vera injections of plasma may be useful, this treatment having the advantage of correcting the hemoconcentration frequent during the first day of life.

Liver extracts and large doses of preparations of vitamin K and ascorbic acid must be given as adjuvants of the treatment with transfusions.

ROJAS, Boston.

PRIMARY ATELECTASIS AND BIRTH TRAUMA. A. ECKSTEIN, Paediat. danub. **1**:20 (Jan.) 1947.

Primary atelectasis in the newborn is invariably due to a central respiratory failure elicited by trauma during delivery. In the case reported such an injury led to a series of symptoms, such as paralysis of the diaphragm on the corresponding side, primary atelectasis causing strain on the heart and pulmonary congestion. Alleviation ensued in two days, though the activity of the diaphragm was not completely restored. Simultaneously, the primary atelectasis and displacement of the heart vanished. Roentgenograms taken during the pathologic condition strengthened the assumption that birth trauma results in small hemorrhages or edema in the neighborhood of the respiration center. The amelioration of these conditions is followed by respiratory improvement. In this case there was paresis of the left half of the diaphragm.

Another newborn infant observed by the author in Düsseldorf, Germany, at an earlier time died. The postmortem examination (Prof. Schleussing) revealed primary atelectasis and hemorrhagic foci dispersed about the nuclear zone of the medulla oblongata. In both cases the causal connection between central injury due to birth trauma and primary atelectasis was evident.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

FATAL INFECTION WITH POLIOMYELITIS VIRUS IN A LABORATORY TECHNICIAN: ISOLATION OF VIRUS FROM LYMPH NODES. HERBERT A. WENNER and JOHN R. PAUL, Am. J. M. Sc. **213**:9 (Jan.) 1947.

The authors report a fatal case of poliomyelitis which occurred in a laboratory worker. It is probable, although not definitely established, that this man acquired his infection as a result of exposure to the poliomyelitis virus in the laboratory.

Prior to his infection he had been working with human infectious material and with strains of the poliomyelitis virus in their early passage in monkeys.

In this case the poliomyelitis virus was isolated during life from the throat and at autopsy from the central nervous system, the washed wall of the duodenum, the mesenteric lymph nodes and some of the lymph nodes in the right axilla. Attention is called to its occurrence at the last site because just prior to the man's illness he had sustained an injury to his skin on the right wrist.

Previous experiences, both published and unpublished, of the isolation of the poliomyelitis virus from lymph nodes are reviewed and discussed in the light of the observations in the aforementioned case.

FROM THE AUTHORS' SUMMARY.

THE ELIMINATION OF POLIOMYELITIS VIRUS FROM THE HUMAN MOUTH OR NOSE. ROBERT WARD and BURRILL WALTERS, Bull. Johns Hopkins Hosp. **80**:98 (Jan.) 1947.

Poliomyelitis virus was detected in the masks of 2 of 19 patients. In 1 of these patients it was also recovered from the nasal swabs and in the other from the pharyngeal swabs. In 5 additional patients virus was isolated from the pharyngeal swabs alone. This is an important demonstration, but its epidemiologic significance is not clear.

LYTTLE, Los Angeles.

MENINGOCOCCAL ADENITIS. RANDALL D. NYMAN and JOHN W. BRUECK, New Orleans M. & S. J. **99**:274 (Dec.) 1946.

A case is reported which, in the authors' opinion, is the first of suppurative meningococcic adenitis presumably secondary to chronic meningococcemia. The isolated organism was Meningococcus type I. Cultures of the blood did not yield the organism.

BERKLEY, Beverly Hills, Calif.

ELECTROCARDIOGRAPHIC CHANGES IN MALIGNANT DIPHTHERIA. P. GIRAUD, A. JOUVE, J. SENEZ and A. HEURTEMATTE, Presse méd. **41**:570 (Sept.) 1946.

Electrocardiographic changes are frequent during the course of malignant diphtheria and may be useful as guide posts to prognosis. At the onset of the disease, sinus tachycardia, which is reduced during the course of the illness, is present. Nodal rhythm is intensified, and auriculoventricular dissociation appears. The T waves become flat and may disappear. From the fifth to the twelfth day, the more serious complications appear. Bundle branch block is one of these and may be preceded by a prolongation of the P-R interval. Although some toxic cases present no graphic changes, daily electrocardiograms should be taken because of the changeable character of the findings.

DAFFINEE, Melrose, Mass.

Acute Infectious Diseases

THE TREATMENT OF ACUTE RHEUMATIC FEVER IN YOUNG ADULTS. HARRY A. WARREN, Illinois M. J. **91**:24 (Jan.) 1947.

Eighty-two per cent of the author's patients had had some type of respiratory infection preceding the onset of rheumatic fever. Epidemiologic studies over a three year period showed that the peak incidence of rheumatic fever occurred one to two weeks after the peak incidence of scarlet fever and other hemolytic streptococcic diseases. Each year the greatest number of cases of rheumatic fever occurred during April or March, with cases scattered from the latter part of November through June.

Patients with rheumatic fever should be carefully protected from streptococcic respiratory disease. Hospital personnel should be checked to eliminate carriers of group A streptococci. No one, relatives or visitors, with a respiratory infection should be allowed in the same room with a rheumatic patient. Oiling of blankets and floors will reduce the incidence of respiratory diseases.

An optimal intake of adequate, nourishing food is an important factor in treatment. Rest in bed is the most important part of the treatment so long as there is evidence of active rheumatic inflammation. There is no specific drug for the disease. All that can be expected of salicylates is relief of joint symptoms and lowering of fever. Large doses of salicylates offer only two advantages: (1) the fever is reduced more quickly and (2) there is more rapid relief of symptoms in acute pericarditis. Salicylates given intravenously offer no advantages over oral therapy. Large amounts of salicylates may lead to serious toxic reactions. Moderate hypoprothrombinemia which may occur with large doses of salicylate is not of major clinical significance. The use of vitamin K is not necessary. The sulfonamide drugs and penicillin are no benefit in the treatment of the active disease.

One gram of sulfadiazine daily will diminish the incidence of streptococcic respiratory diseases. Patients with rheumatic heart disease should receive sulfonamide prophylaxis if they live in an area where streptococcic infections are frequent. Sulfonamide drugs and antibiotic substances offer no protection once the streptococcic infection is established.

BARBOUR, Peoria, Ill.

KALA-AZAR IN INFANCY. M. BERNHEIM and M. VIALTEL, Presse méd. **54**:393 (June 15) 1946.

The authors present a case of kala-azar in a child of 3 years. The etiologic agent was a dog tick, which bit the child on the head. Leishman-Donovan bodies were found in the smears from sternal puncture. Cure was effected by the use of an antimony compound.

DAFFINEE, Melrose, Mass.

ROUNDWORMS SEEN ON ROENTGENOGRAM. JAN BORES, Pediat. listy **1**:170, 1946.

The value of roentgenographic examination and the technic used in the diagnosis of intestinal parasites are stressed. Roentgenograms are shown.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

HEREDITARY (SEX-LINKED) ANEMIA. R. WAYNE RUNDLES and HAROLD F. FALLS, Am. J. M. Sc. **211**:541 (June) 1946.

A hypochromic microcytic anemia with deformed erythrocytes, splenomegaly and sometimes hepatomegaly, affecting the male members of 2 families through several generations, is described. The disease appears to be transmitted from generation to generation by the female members of the family, many of whom have enlarged spleens and minor abnormalities of the red blood cells without anemia, in a manner compatible with sex-linked inheritance in which the abnormality is recessive in women.

The general problem of the atypical hereditary anemias is discussed.

HENSKE, Omaha.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY: I. APLASTIC ANEMIA ASSOCIATED WITH SULFONAMIDE THERAPY. HELEN M. DENNY and MAUD L. MENTEN, Am. J. M. Sc. **211**:659 (June) 1946.

The authors describe 6 cases of aplastic anemia associated with sulfonamide therapy. In 4 of these cases sections of bone marrow taken at autopsy revealed an extensive hypoplasia. The depletion of hematopoietic tissue is interpreted as resulting from direct injurious action of the drugs on the cells of the marrow in their early stage of development.

HENSKE, Omaha.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY: II. GRANULOCYTOPENIA ASSOCIATED WITH USE OF SULFONAMIDES. MAUD L. MENTEN and ESTHER GRAFF, Am. J. M. Sc. **211**:666 (June) 1946.

An analysis of the cases of granulocytopenia with less than 3,000 cells per cubic millimeter occurring in the first quarters of the years 1936 to 1945 inclusive revealed that they constituted 3 per cent of the total number of admissions before the use of the sulfonamide compounds and then assumed a gradually increasing incidence paralleling the increased use of those drugs. The incidence reached a maximum of 12 per cent in 1944, when medication with sulfadiazine was being used most widely, and diminished to 7.6 per cent in 1945, when penicillin replaced much of the sulfadiazine. The percentage of cases of neutropenia developing from sulfonamide compounds in these two years, however, remained the same, namely, about 20 per cent of all cases in which the drug was administered.

FROM THE AUTHORS' SUMMARY.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY: III. TREATMENT OF GRANULOCYTOPENIA WITH FOLIC ACID AND PYRIDOXINE HYDROCHLORIDE. MAUD L. MENTEN and ESTHER GRAFF, Am. J. M. Sc. **211**:672 (June) 1946.

Of 22 children and 1 adult in whom granulocytopenia had developed after sulfonamide therapy, 13 showed a favorable response in the granulocyte count after treatment with the Lactobacillus casei factor (folic acid [pteroylglutamic acid]). Pyridoxine hydrochloride was used as an adjuvant to the L. casei factor in treatment of many children. White blood cell counts made on 9 of the 13 children at various periods after treatment indicated that the increase in granulocytes obtained with the L. casei factor was maintained in half of the children only. The low initial response, as well as the subsequent variation in the level of granulocyte values, is believed to have been due to inadequate dosage with the L. casei factor.

FROM THE AUTHORS' SUMMARY.

CHANGING CONCEPTS IN MEDITERRANEAN (COOLEY'S) ANEMIA. IRVING J. WOLMAN and BENJAMIN DICKSTEIN, Am. J. M. Sc. **212**:723 (Dec.) 1946.

The authors review the literature of the terminology, carrier state, etiology, diagnostic criteria, prevalence and distribution and prognosis and treatment of familial erythroblastic anemia (Mediterranean [Cooley's] anemia), with the following conclusions: The observations summarized represent a body of information impressively elaborate when one considers that the disease was not recognized as an entity until two decades ago. Numerous problems related to it are as poorly understood now as when Cooley and Lee made their first report. The basic defect has an inherited origin and probably is more closely related to the formation of red cells than to that of hemoglobin (though both seem defective in advanced cases), but its precise nature is not known. The recognition of the carrier state represents a major step forward, of as great importance to adult as to pediatric medicine, and yet the mechanism of genetic transmission has become more, rather than less, obscure as a consequence of this discovery. Valentine and Neel's estimate of 1 affected carrier per 25 persons of Italian origin calls for corroboration. Adequate knowledge regarding heredity is necessary in order for one to be able to give eugenic advice to young couples when one or both are found to carry the trait. Treatment, of course, has always been highly unsatisfactory, palliative transfusion being the only helpful procedure known. Widespread attention should be given to Koteen and Brooks's experience in an outpatient transfusion clinic. If transfusions can be given to patients with the active disease in outpatient

departments at frequent regular intervals, the rate of infections will decrease, the costs to hospitals will diminish and the children themselves will fare better.

FROM THE AUTHORS' SUMMARY.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE: I. PROCEDURES; II. RESULTS OF PREOPERATIVE STUDIES IN PATIENTS WITH TETRALOGY OF FALLOT. R. J. BING, L. D. VANDAM and F. D. GRAY JR., Bull. Johns Hopkins Hosp. **80**:107 (Feb.) 1947.

The first paper describes the technical procedures employed in the study of congenital heart diseases belonging to the cyanotic group. Some of the data obtained were used for calculating blood flow through the lungs and the systemic circulation, and for estimation of the volume and direction of extracardiac and intracardiac shunts. The physiologic and diagnostic values of these procedures are discussed, with the realization that the calculations involve assumptions which may not be valid, so that the results should be looked on as no more than approximations.

In the second paper, the results of physiologic studies in 48 consecutive cases of tetralogy of Fallot are presented. These papers are not easy to abstract and should be read by those interested.

LYTTLE, Los Angeles.

SOME CORRECTIBLE ANOMALIES OF THE HEART AND GREAT VESSELS. S. P. WISE III, New Orleans M. & S. J. **99**:280 (Dec.) 1946.

The author gives a good review and bibliography of recently described diagnostic aids and surgical procedures now applicable to certain anomalies of the heart and great vessels.

BERKLEY, Beverly Hills, Calif.

PERNICIOUS ANEMIA (BIERMER'S DISEASE) IN A CHILD TWO YEARS OF AGE. M. KAPLAN and JEAN-BERNARD, Arch. franç. de pédiat. **3**:161, 1946.

This case was reported in minute detail before the Pediatric Society of Paris on Jan. 15, 1946. The disorder of the blood known in France as Biermer's disease, synonymous with pernicious anemia, has rarely been observed in early childhood.

The current presentation concerned a girl 2 years of age, a twin whose brother had died at 7 months of age of mastoiditis. Examination at the Hospital for Sick Children, Paris, France, revealed extreme pallor with a slight trace of jaundice; the conjunctivas and the lingual mucosa were colorless. Emaciation was not pronounced, the weight being 10.5 Kg. for the height of 835 cm., but exhaustion was profound.

Dyspnea, edema, abnormal pigmentation, area of purpura and other evidences of hemorrhage were all absent; there was no fever, nor buccal or lingual ulceration. Total anorexia existed without vomiting, but with obstinate constipation. Muscular strength and tonus were normal, as were the tendon reflexes; the mental examination revealed nothing uncommon. There was no trophic disturbance, no adenopathy and no abnormalities of the spleen or liver. Roentgenographic studies showed nothing abnormal. Examination of the blood revealed 656,000 red cells; a hemoglobin content of 20 per cent, and 6,400 white cells per hundred cubic centimeters, of which 33 per cent were polymorphonuclear neutrophils, many with 7, 8 and even 10 nuclear segments; 3 per cent eosinophils; 47 per cent small lymphocytes, 6 per cent large lymphocytes and 8 per cent monocytes.

Further studies of the blood showed anisocytosis with frank megalocytosis: smears demonstrated oval megalocytes with a diameter of 12 millimicrons, microcytes and schizocytes, moderate poikilocytosis and polychromatophilia. One megaloblast

could be seen for every 100 leukocytes. The globular resistance was reduced. The blood group was O Rh+ (Bessis).

A study of the osseous marrow showed severe medullary megaloblastosis. The gastric juice had free hydrochloric acid, with total acidity of 4 degrees; half an hour after the injection of histamine, there was free hydrochloric acid of 14 degrees, with total acidity of 27 degrees.

Treatment, consisting of daily intramuscular injections of an active hepatic extract of 2 to 5 cc. each, together with transfusions, transformed the subject, and progress toward recovery was uninterrupted. The authors call attention to the fact that achylia is not necessarily present in pernicious anemia of young children.

AMESSE, Denver.

Diseases of Nose, Throat and Ear

ROENTGENOLOGIC DIAGNOSIS OF AURAL DISEASES IN INFANTS. C. GEFFERTH, Paediat. danub. 1:41 (Jan.) 1947.

A procedure is presented by which both mastoid cavities are shown on the same roentgenogram. During exposure the infant lies on his back, a position which is natural. The rays are made to fall from behind in an angle of 10 to 15 degrees to the nasion. Pneumatization of the antrum can readily be shown by this method.

Several other conditions were also diagnosed by this technic. A case of a cyst in the mastoid process and another of inadequate antrotomy, which were revealed with its aid, are presented.

FROM THE AUTHOR'S SUMMARY.

PENICILLIN AFTER ANTROTOMY: EFFECT IN INFANTS AND CHILDREN. E. GYÖRGY, Paediat. danub. 1:46 (Jan.) 1947.

Twenty-eight infants and children were operated on for acute mastoiditis, and the wounds were immediately closed. The procedure in antrotomy and after-treatment was as follows: Great care was taken to remove all the diseased parts of the bone and to control hemorrhage. The area of operation was then cleansed with penicillin solution; a few drops were injected into the tympanic cavity and some left in the antrum. The wound was then closed with clips, and penicillin was instilled into the typmanic cavity through the auditory canal. Following this, a single dose of 10,000 units of penicillin was administered intravenously. Subsequently, intramuscular doses of 5,000 to 10,000 units were given every three hours for three consecutive days. In two days, some of the clips were removed and the remaining ones two days later. Complete recovery took eight to ten days in 24 of the 28 cases. Hemorrhages were noticed in 4 children, while in 4 others the drug had no effect.

FROM THE AUTHOR'S SUMMARY.

Diseases of Lungs, Pleura and Mediastinum

BRONCHOSCOPY AS AN AID IN THE DIAGNOSIS OF PULMONARY DISEASES. PAUL H. HOLINGER and ALBERT H. ANDREWS JR., Illinois M. J. 91:12 (Jan.) 1947.

Important changes have occurred in the management of pulmonary suppuration, neoplastic disease, tuberculosis and certain cardiac conditions during recent years. These changes are principally the results of, first, improvements in technic of thoracic surgery in treatment of pulmonary suppuration, neoplasms, tuberculosis and cardiac anomalies; second, the recognition of the importance of bronchial tuberculosis, and, third, the great advances in chemotherapy.

The sulfonamide drugs and penicillin have increased the effectiveness of treatment of pulmonary suppuration; however, at the same time, they have inter-

posed certain diagnostic problems by contributing seriously to the masking of symptoms and findings. The principle of drainage of suppuration may be overlooked because of clinical improvement produced by the administration of these chemotherapeutic agents.

Bronchoscopy has both a diagnostic and a therapeutic role in the management of pulmonary suppuration. In pulmonary suppuration penicillin by inhalation has given surprisingly good results. The occurrence of tracheobronchial tuberculosis affects the prognosis and treatment of the parenchymal lesion. Bronchoscopy is indicated if there is a suspicion of endobronchial involvement. From bronchoscopy one obtains the following information: type of lesion, location, extent of the lesion and presence or absence of bronchial obstruction. Treatment of the lesion or of the obstruction may be done through the bronchoscope. Great advances have been made in the surgical treatment of bronchogenic carcinoma. Early diagnosis is essential. Bronchoscopy is of major importance in the early diagnosis.

BARBOUR, Peoria, Ill.

STAPHYLOCOCCUS PNEUMONIA IN CHILDREN: ROENTGEN ASPECTS. W. E. ANSPACH, Illinois M. J. **91**:75 (Feb.) 1947.

Of 40 cases of staphylococcus pneumonia at Children's Memorial Hospital, Chicago, 33 came to necropsy. All but 2 cases showed changes on roentgenograms of the chest which were strikingly similar. In all but 1 of the necropsy group, Staphylococcus aureus was demonstrated to be the only or the predominating organism.

The blood-borne type of staphylococcus pneumonia is that of miliary distribution scattered evenly throughout both lungs. Each of these cases followed a severe cutaneous infection, usually with furuncles, and all patients died before abscess cavities could be seen on roentgenograms of the chest. Roentgenographic signs which strongly suggest a staphylococcus infection cannot be said to be diagnostic, but often favor this diagnosis. The commonest staphylococcus pneumonia is associated with fibrocystic disease of the pancreas and should arouse suspicion of that disease.

The bronchogenic type of staphylococcus pneumonia, which often is a complication of foreign material in the lung, follows other pulmonary diseases, such as influenza, or follows, sooner or later, the less resistant bronchial mucosa and the presence of thick secretions in fibrocystic disease of the pancreas. The latter is the most fatal and the commonest and accounts for many of the deaths in this series.

BARBOUR, Peoria, Ill.

CHRONIC COUGH IN CHILDREN. R. V. PLATOU, New Orleans M. & S. J. **99**:270 (Dec.) 1946.

Chronic cough is a common pediatric problem. The author urges that it be given the amount of study to which it is entitled. The tendency is to treat too much and to seek too little. The chronic cough often does not fit a pathognomonic pattern, fails to respond to ordinary therapy and frequently receives less than deserved attention. The list of possible causes is long and increases in proportion to the care of the clinical study. Physicians tire of the diagnostic challenge and often resort to medication to suppress the cough, regardless of the cause.

A careful study will almost always furnish clues to the correct diagnosis. The physical examination should be carefully done, special attention being directed to the nasal sinuses. The laboratory work in appropriate cases should include a tuberculin test, roentgenographic examination of the chest, blood count, determi-

nation of sedimentation rate and culture of nasal and pharyngeal smears. Even examination of stools for parasites is necessary in some cases.

If cystic disease of the pancreas is suspected, the duodenal enzymes should be investigated.

BERKLEY, Beverly Hills, Calif.

Nervous Diseases

STREPTOCOCCUS VIRIDANS MENINGITIS WITH PNEUMONIA. FRANKLIN A. KYSER, Illinois M. J. **91**:81 (Feb.) 1947.

A case of Streptococcus viridans meningitis with recovery is reported. Associated pneumonia was probably caused by the same organism.

BARBOUR, Peoria, Ill.

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS: THREE PATIENTS CURED WITH SULFADIAZINE AND ANTI-INFLUENZA TYPE B RABBIT SERUM. F. C. MILIA, Arch. argent. de pediat. **26**:81 (Aug.) 1946.

The author reviews the present knowledge about Hemophilus influenzae meningitis. His results and those reported in the world literature lead him to affirm the superiority of the combined treatment (Alexander's scheme) to the others and to stress the necessity that the anti-influenza type B rabbit serum be available to all people in Argentina. He proposes a laboratory test, with the aim of determining the sensitivity of the causal strain to penicillin and so demonstrating the actual efficiency of using that drug in combination with sulfonamide drugs, as has been recently proposed.

FROM THE AUTHOR'S SUMMARY.

EPILEPSY AND CONVULSIONS IN INFANCY. RICARDO OLEA G., LUCIA CAPDEVILLE, FERNANDO SANHUESA and CELIA PAVEZ R., Arch. d. Hosp. de Niños Roberto del Rio **13**:-147 (Dec.) 1945.

Each copy of this journal is in the form of a monograph on some subject. In the introduction to this paper on epilepsy, the senior author points out that, in general, the definitions and classification of Wilson are utilized in his clinic. He states in advance that all epilepsy can be considered symptomatic, those cases in which the cause is as yet obscure being called cryptogenetic. He considers first the frequency of epileptic onset in infancy. Two sources of confusion in this regard are the improper classification of convulsions accompanying toxic and infectious febrile states and the erroneous diagnosis of spasmophilia. He feels that there is some latent convulsive predisposition in children with occasional febrile convulsions and that the term spasmophilia, which should be synonymous with tetany as in convulsions, has been applied loosely. For these reasons, epilepsy and latent epileptic states are more frequent in infancy than generally supposed.

In the second part of the monograph, Dr. Capdeville discusses the clinical forms of the disease. Utilizing the Wilson classification she gives illustrations for the various types from the Hospital Roberto del Rio. A most interesting observation is included in 1 case record illustrating the visceral type of epilepsy. This patient, who had had seizures every two weeks since the age of 5 months, contracted measles at 2 years of age and thereafter for a period of six months was free from attacks and had definite activation of intelligence. At the end of this period, the attacks returned, and intelligence retrogressed notably.

In the third part of the paper, Dr. Sanhuesa discusses the psychic manifestations of epilepsy in children. In order that the data represent only the manifestations of cryptogenetic epilepsy, he carefully ruled out all cases with toxic, in-

fectious and degenerative disease primary to seizures. Of the 3,100 cases seen in the clinic with convulsions, 331 were considered cryptogenetic, an incidence of 10.6 per cent. He gives a good discussion of prodromes, auras, immediate and remote sequelae and the so-called epileptic personality.

In the fourth part of the paper, Dr. Pavez tabulates the etiologic considerations in these cases. Age, sex, family history, past history and frequency of attacks are all nicely presented in tabular form so that they can be easily studied.

The monograph as a whole is instructive, being well interspersed with illustrative case histories.

MILLER, Newark, Ohio.

Skin Diseases; Allergy

EDEMA OF UNKNOWN ORIGIN. LEIF SALOMONSEN, Nord. med. (Norsk mag. f. laegevidensk.) **25**:727 (March 29) 1945.

The author reports a case of chronic general edema of varying intensity in a child 4 years of age. Hypoproteinemia (total serum protein measured 2.54 to 3.5 mg., serum albumin 1.19 to 1.74 mg. and serum globulin 1.35 to 1.78 mg., per hundred cubic centimeters) was present, with 392 mg. of chloride and 327 mg. of sodium per hundred cubic centimeters. The cause of the hypoproteinemia was unknown. The kidneys, heart, intestine and endocrine glands were normal. No deficiency disease was apparent. The author is of the opinion that his case corresponds to that of Thompson, McQuarrie and Bell (*J. Pediat.* **9**:604, 1936) in which the hypoproteinemia was probably due to atrophic changes in the liver.

WALLGREN, Stockholm, Sweden.

Book Reviews

Synopsis of Pediatrics. By John Zahorsky, M.D., assisted by T. S. Zahorsky, B.S., M.D. Fifth edition. Pp. 449, with 158 text illustrations and 9 color plates. Price, $5. St. Louis: C. V. Mosby Company, 1948.

Dr. Zahorsky presents a well organized and detailed compendium of pediatrics. Chapters XLIV, XLVI and XLVII deal justly and practically with the diseases of the respiratory organs, including the ear, the nose and the throat; chapter XX describes the common cold, common grip and influenza. Color plates illustrate tonsillar diphtheria (plate III), scarlatinal throat and tongue (plate IV), lacunar tonsillitis, follicular tonsillitis (plate VIII) and Vincent's angina (plate IX).

Impressions relative to the nature of the lymphoid tissue occurring in the nasopharynx in childhood may be summarized as follows:

Acute pharyngitis is most frequently a part of the pathologic process of infections of the upper respiratory tract. It is a forerunner of the common head cold (most common disease occurring in children). True influenza begins with definite congestion of the blood vessels of the lateral walls of the pharynx. Pharyngitis is a part of the lesion of the throat in many infectious diseases, such as measles, scarlet fever, diphtheria, septic sore throat and tonsillitis.

Acute adenoiditis is commonly secondary to acute pharyngitis and usually associated with a tonsillar infection. Occasionally this inflammatory process is limited to the adenoids. The general symptoms are the same as those of tonsillitis, but the characteristic sign is a sudden occlusion of the nasal passages not due to intranasal swelling as in the common cold.

Because an acute infection of the adjacent structures frequently precedes the tonsillar reaction, the author believes that the tonsils are infected most often from the submucosal spaces in the lateral wall of the pharynx. It is difficult to explain the simultaneous reaction of both tonsils and adenoids on any other ground. Like all submucosal follicles, the tonsils continually absorb septic material from the surrounding parenchyma, especially the lateral wall of the pharynx. The author therefore regards the gradual enlargement of the tonsils of early childhood as a defensive adjustment. The tonsils begin to atrophy as soon as the general and the local resistance have increased by immunologic processes (six to eight years).

He does not consider enlarged tonsils as causative of repeated colds, bronchitis, croup, otitis media, periodic vomiting or asthma. The susceptibility to these diseases is constitutional rather than local and varies in severity in different families. Enlarged cervical glands are more commonly associated with infections of the mucous membranes than with those of the tonsil.

He states that for children less than 6 years of age the treatment of enlarged and infected tonsils is primarily medical. The following indications for removal are set forth: (1) frequently recurring tonsillitis; (2) persistent enlargement and congestion of tonsils not responding to careful medical treatment; (3) clinical evidence that the infected tonsil is either so embedded or so much scarred that it cannot discharge its septic contents readily during an attack of tonsillitis, and (4) protracted obstruction to respiration.

Physician's Handbook. Fourth Edition. By John Warkentin, Ph.D., M.D., and Jack D. Lange, M.D. Price, $1.50. Pp. 282, with illustrations. Chicago: University Medical Publishers, 1946.

The "Physician's Handbook" is an amazingly complete manual, which could serve as a most convenient pocket reference until more complete sources of material may be consulted. However, the scope of the volume precludes the possibility of emphasis on, or completeness of, information pertinent to any particular specialty. This limitation particularly applies, in the reviewer's opinion, to pediatric coverage. It would seem that the "Handbook" would serve best at the intern and resident level and for the physician in general practice.

The excellent exposition of clinical tests and laboratory procedures, as well as the tabulation of a wide variety of normal values, is undoubtedly the most useful feature of the book.

Office Immunology: Including Allergy. Edited by M. B. Sulzberger, M.D., and R. L. Baer, M.D. Price $6.50. Pp. 420, with 20 illustrations. Chicago: The Year Book Publishers, Inc., 1947.

This volume contains a compilation of procedures in the clinical practice of allergy. Pediatricians are sufficiently well versed in the various cutaneous tests and are familiar with the antigens used to establish immunity against the common infectious diseases. The volume can hardly appeal to those who have most of the subject matter at their finger tips, but it would be of value to the busy general practitioner, who has to thumb through many leaflets to find what he wants. However, the book will have to be revised frequently to keep it up to date. For the pediatrician, most systems of pediatrics are better references.

Microbial Antagonisms and Antibiotic Substances. Second Edition. By Selman A. Waksman, Ph.D. Price, $4. Pp. 415, with 33 illustrations. New York: The Commonwealth Fund, Division of Publications, 1947.

The introductory chapters are a summary of the environmental factors which influence the microbiologic population in soils and water basins. It is emphasized that, in the struggle for existence among micro-organisms, one species may gain ascendancy by the production of substances detrimental to the growth of other species. Some of these substances have been isolated and designated as antibiotic. The remainder of the book is principally a review of the literature concerned with the various properties, chemical compositions and modes of action of these substances. Some antibiotics are of only theoretic interest. Others, especially penicillin, streptomycin and tyrothricin, have additional interest because of their effectiveness in the treatment of certain infectious diseases of plants, animals and human beings. The study of these materials, and of the innumerable others, not yet isolated in purified form from their natural sources, has led the author to conclude with good reason that the work on antibiotics has just begun.

The author has compiled and reviewed an extensive, complex literature on antibiotics in a comprehensive manner. This completeness has led to many repetitions, often unavoidable in reviews of this type. It might have been better if fewer data had been presented in detail and more of the material handled by brief critical analysis. Furthermore, many readers doubtless will feel the lack of pertinent comparisons of modern organic chemotherapeutic agents and antibiotics. If such a comparison had been made, it would have led to a clearer

understanding of the trends in the bacteriology, immunochemistry and therapeutics of infectious diseases.

Milk and Food Sanitation Practice. By H. S. Adams, Ph.D. Price, $3.25. Pp. 311, with 9 tables, 65 illustrations and appendix. New York: The Commonwealth Fund, Division of Publications, 1947.

This book, intended for use by the public health student interested in the field of environmental sanitation, and as a guide for public health workers generally, is divided into two sections.

The first section treats the problems of milk sanitation; the second, those of food sanitation. Both sections are complete and valuable as text and reference material for specialists in milk and food sanitation and in allied fields. For pediatricians, the book is not of special interest, except for one who would like to know, for example, about safe milk production, the cause of undesirable flavors in milk and how to meet common objections to pasteurization.

In the section on food, the discussion in the appendix on "Food Poisoning and Infections" should be of interest to the pediatrician.

The work is well written and contains a good bibliography.

Clinical Practice in Infectious Diseases; for Students, Practitioners and Medical Officers. Third edition. By E. H. R. Harries, M.D., and M. Mitman, M.D. Price, $6. Pp. 679, with 42 illustrations. Baltimore: Williams & Wilkins Company, 1947.

A number of excellent books on contagious diseases have appeared in recent years, but there seems to be none that is quite the equal in completeness to this of Harries and Mitman. The third edition has been revised and expanded considerably by an additional chapter on the pneumonias and short descriptions of a number of other conditions, including the common cold, epidemic myalgia and infective polyneuritis.

In the opening chapter there is a discussion of the meaning of the terms "contagious" and "infectious," as well as one of certain public health regulations which are established by law. The authors point out that in Great Britain "infectious" is used to denote the diseases which in this country we call contagious, or communicable.

The well written chapters on infection and resistance; hypersensitiveness, allergy and serum reactions; transmission; diagnosis, and epidemiology, which comprise the first 100 pages, prepare the student for a better understanding of the descriptions of the individual diseases that follow. A synopsis of the contents is presented at the beginning of every chapter.

Toward the close of the book are three chapters relating to the management of infectious diseases. They explain all phases of treatment, with detailed descriptions of the sulfonamide compounds and penicillin. The thirty-eighth, and final, chapter is titled "Control of Infectious Diseases in Hospital."

In agreement with the opinion of other British authorities, the authors have deliberately omitted the inclusion of photographs representing the exanthems. This action is based on the belief that such illustrations frequently convey a misconception of the true appearance of the disease and, therefore, are a detraction. There are, however, 28 tables, numerous diagrams and abundant references at the close of each chapter.

Thoroughly revised to date, this edition, even more than its predecessors, should be, of great value to the teacher, practitioner and student.

The Acute Infectious Fevers. By Alexander Joe, M.D. Price, $4.50. Pp. 276, with illustrations. Philadelphia: The Blakiston Company, 1947.

This textbook is a compendium in the 276 pages of which are discussed those types of diseases that are ordinarily treated in what the British call a fever hospital. There are fifteen chapters and fifteen subjects. The usual diseases treated in an American hospital for contagious diseases are covered.

Information of this type in the United States is usually found in comprehensive textbooks on medicine and pediatrics, in which subjects are covered, not always to their best advantage, by many authors. This text is a fundamental presentation of accepted ideas, the author preferring not to philosophize; as a consequence, though an adequate presentation, it is drier reading than that found in the usual British textbook.

It contains nothing not included in the usual systems of medicine.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Bornehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associacao Paulista de Medicina, Seccao de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjorup, Dronning Louises Bornehospital, Copenhagen.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft fur Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela Deheza, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., Second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez Cèsar, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre, Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÈTÈ DE PÈDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7°, France.
Secretary: Dr Maurice Lamy, 94 rue de Varenne, Paris 7°, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenda Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

American Academy of Pediatrics

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlanta, Ga. Time: April 13-15, 1949.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

American Hospital Association, Massachussetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Wm. D. Rothwell, Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel, Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

Arizona Pediatric Society

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

Louisiana State Pediatric Society

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

Medical Society of the State of New York, Pediatric Section

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St.. Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Walter R. Coles, 604—2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granda Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Forth Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Forth Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders, Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708-15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A., Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).